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URETERAL STRICTURE: THE ETIOLOGY, DIAGNOSIS, PATHOLOGY AND TREATMENT OF A NEW ABDOMINAL SYNDROME.*

By Guy L. Hunner, M.D.,

ASSOCIATE PROFESSOR IN CLINICAL GYNECOLOGY, JOHNS HOPKINS UNIVERSITY MEDICAL SCHOOL.

Skepticism and the adoption of a new idea only after a reasonable demonstration of its practical value are signs of a healthy attitude in medical practice. Rejection of a theory because of its novelty or because its acceptance leads to the overthrow of traditional views and practice may indicate a state of smugness or self-complacency which in some fields may be condoned without argument, but which in medicine may cause serious injury to the patient, who has entrusted the physician with the care of his health.

Although Fitz of Boston published his epoch-making paper on appendicitis in 1886, some of us are old enough to remember many shocking disasters occurring in the early years of this century because in the minds of some medical men acute appendicitis was still a novel idea and looked upon almost as an obsession of the surgeons. Indeed, it was only when the layman had experienced some of these disasters in his own, or in his neighbor's family, and had thus learned to suspect acute appendicitis and to carry his case direct to the surgeon, that some of the more conservative members of our profession awakened and added this disease to their daily reckoning with acute abdominal disorders. But, although,

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fortunately the disease whose syndrome we are discussing rarely leads to such immediate disasters as so often occur in cases of acute appendicitis, it is certain that ureteral stricture is an abdominal disease of sufficient importance to warrant our making some comparisons between the two conditions.

As a gynecologist, I naturally have far fewer appendicitis patients referred for diagnosis and treatment than the general surgeon, and I am not in a position to judge from personal experience regarding the relative incidence of this disease. As yet our hospital records are not helpful in comparing the incidence of ureteral stricture with that of appendicitis, because in most hospitals ureteral stricture is not being systematically diagnosed.

Because of the early diagnosis and surgical treatment of most cases of appendicitis, and because of the neglect of proper diagnosis in most patients suffering with ureteral stricture, one is justified in stating that today ureteral stricture as a source of incapacity and morbidity ranks equally with or perhaps above appendicitis. Ureteral stricture as treated, or rather, as neglected today, is not only responsible for the physical discomfort and incapacity which it directly causes, but must also be charged with the results of mistaken diagnoses. To make this plain, I need present only a partial list of the evil consequences following our neglect of this disease. On the economic side, there is tremendous loss in disability, time, and hospital expense incurred in following various lines of treatment founded on erroneous diagnosis. When such errors lead to multiple abdominal operations, the patient not only suffers the undermining of the nervous system consequent on the operations and repeated disappointments in obtaining results, but she is likely to acquire permanent morbid processes as a result of the operations. And, finally, if we need further presentments to make the indictment impressive, let us add the last and most important count, namely, the resultant damage to the kidney when we fail to make an early diagnosis of ureteral stricture. In the face of these indisputable facts, can, then, the members of our profession in these days of preventive medicine still continue to contemplate these mistakes with equanimity?

At the risk of making my paper seem elementary after all that has been written on the subject, I shall try to help the busy general practitioner to bear in mind the possibility of the existence of this disease in doubtful cases by presenting a brief summary of its etiology and symptomatology in women, founded on an experience with more than 2500 cases studied in the past fifteen years.

Definition. Ureteral stricture is an intrinsic disease of the ureteral wall resulting in narrowing of the lumen, which leads to varying degrees of stasis in the urinary stream.

Etiology. This narrowing may be congenital or acquired. The congenital types probably most often represent anomalies of devel-

opment, but I believe that time and more careful study will eventually prove that some of the congenital cases are caused by inflammatory processes derived through the placental circulation. By far the greater number of ureteral strictures, however, are acquired. We see an occasional stricture of traumatic origin either from a severe accident, a gunshot or stab wound, or from injury at operation or childbirth. Syphilis may be responsible for an occasional case. I have seen one stricture located at the pelvic brim which was apparently secondary to the pressure and inflammatory action of an adherent ovarian cyst. I have seen pressure by uterine fibroids cause hydronephrosis and hydroureter above, but apparently without causing intrinsic disease of the ureteral wall. Adenomyoma as it spreads across the pelvis sometimes involves the ureter causing stasis from encircling pressure. I have never seen a stricture which could be ascribed to the juxtaposition of a pus tube. A fairly large group of ureteral strictures are associated with cancer of the cervix. The inflammatory process in these cases may involve the periureteral tissues more than the ureteral wall itself and may be present at the time of operation, or it may follow the inevitable trauma and infection due to operation. In a new group, of which I have seen several examples, the periureteral and ureteral infiltration in the broad ligament region has apparently followed the use of the cautery or radium, before, during or after the operation. In renal tuberculosis, disease of the ureter is often a secondary manifestation.

As a gynecologist, I have been constantly expecting to see stricture in the broad ligament region which could be ascribed to inflammatory disease of the cervix, but thus far I have not been able to trace this connection.

Simple inflammatory stricture due to a focal infection in some other part of the body is so overwhelmingly frequent, when compared to stricture from all other causes, that we are justified in saying that the disease usually originates from some such focus. The acute infectious diseases of childhood probably leave inflammatory areas in the ureter, the results of which may not be apparent until later in life. Any localized acute or chronic inflammatory process may finally lead to ureteral stricture. Carbuncle, onychia, intestinal, gall bladder, appendix, and bone inflammations probably each account for a certain percentage of stricture cases; but my experience seems to point to the infections about the head as causing by far the largest number of inflammatory conditions in the ureteral wall. My reasons for this view are briefly as follows: (1) A careful history often reveals that the symptoms due to stricture began soon after an attack of tonsillitis, sinusitis, or a dental abscess. (2) Experience has taught me that the treatment of the stricture area is often futile until one has located and eradicated infection in one of these areas. (3) Dilatation of the stricture area may result in cessation of all symptoms, and in the clearing up of a pyelitis, if

present, only to have the patient come back weeks, months, or years later because of the return of all the symptoms following a fresh attack of sinusitis, tonsillitis, or dental inflammation, or after a visit to the dentist. (4) After a tonsillectomy on a patient who has had treatment for stricture we occasionally have the patient complain far more of pain in the ureteral and renal regions than of the local discomforts from the operation. A cystoscopy a few days after the tonsillectomy shows, in some cases with such ureteral reaction, a wide area of edema and redness surrounding the ureteral orifice, in contrast to the normal or approximately normal appearance of the mucosa in all previous examinations. (5) During and after the grippe epidemic of 1918, many of my "cured" stricture patients returned for further treatment after a severe attack of grippe. (6) Another reason for considering ureteral stricture as originating from a focal infection is the fact that it practically always occurs bilaterally. From the fact that most strictures occur in the broad ligament region from 2 to 5 cm. above the bladder, or in the iliac-gland region from 3 to 5 cm. below the pelvic brim, I have advanced the theory that the systemic infection or toxin probably first attacks the lymphatic glands in these regions and later invades the neighboring ureteral wall.

Symptomatology and Diagnosis.—Because our attention has but recently been called to this disease, the general practitioner is likely to consider that it is of rare occurrence and that its symptoms are so vague as to make a diagnosis difficult and available only to the specialist. As a matter of experience, the physician who keeps this disease in mind, when considering any vague abdominal disorder, is surprised at the frequency of its occurrence, and at the ease with which a fairly certain diagnosis is made without the aid of the urologist.

The urologist who is treating ureteral stricture constantly marvels at the number of patients who come to him on the recommendation of other patients, whom he has relieved, and who recognize the symptoms in their friends and send them for treatment over the head of the family physician, who has failed to make a diagnosis; thus repeating the history of what happened in the early days of appendicitis work.

It would be offensive even to hint that the general practitioner is incapable of making a reasonably certain diagnosis in most cases of chronic gall-bladder disease or appendicitis without calling a specialist to help; but careful anamnesis and physical examination in a case of ureteral stricture usually furnish far more clues for an accurate diagnosis than are obtainable in the above two diseases. Probably every man with a reasonably large practice has one or more of these patients on his visiting list, patients who for the most part have been consigned to the group of neurasthenics supposedly in the enjoyment of miserable health. Some of these patients

are decorated with a half dozen abdominal scars, mute or painful testimony to the zeal of surgical and gynecological brethren, who have been trying to aid in making a diagnosis. Others have tried the patience and skill of gastrological confrères and are still complaining of the vague abdominal pains, the accumulations of gas, or perchance a continued mucous colitis. Others are wearing the harness of orthopedic colleagues in a fruitless effort to relieve the back, hip and thigh pains. Here and there a rare individual has been sentenced to one or more terms at Saranac, Asheville, or Colorado, in spite of the fact that the most exhaustive clinical methods have failed to reveal signs of tuberculosis, and the patient still complains of a vague indefinite backache located higher than the usual kidney ache, a slight daily rise of temperature, and general malaise and asthenia.

And yet the general practitioner, if he so wills, can learn tomorrow, almost to a certainty, and without the help of a urologist, whether or not one of these trying patients has ureteral stricture as the physical foundation for the so-called neurasthenic condition.

Careful anamnesis elicits in about 75 per cent of these cases a history of bladder trouble. This may be so slight that the patient has not mentioned it, and on the direct question may answer that she has no bladder symptoms, only a slight frequency when she gets nervous or excited, or a frequency at the time of the menstrual period, or in association with a "cold" or sore throat, or with an arthritic attack. From this almost negligible symptom of intermittent frequency, we see all grades of bladder distress up to the condition of complete incontinence of urine in patients in whom we find no other lesion of the urinary tract than a ureteritis, and for whom we obtain perfect relief by dilatation of the ureteral stricture alone, or combined with attention to some area of focal infection if this has not already been treated.

Urinalysis may be most helpful in the diagnosis; sometimes, however, it may be only slightly suggestive, or at times most misleading. In 20 per cent of stricture patients, there is a chronic pyelitis on one or both sides, and the urine will give characteristic findings. In 50 per cent only a few erythrocytes, a few leukocytes, albumin from a slight trace to a large quantity, or casts, or a combination of these elements will be found. Too often in the past such evidences of disease, when found in meager quantity and only on the most painstaking urinalysis, have been considered as of no significance. In the remaining 30 per cent of stricture cases, the urinalysis is completely negative and patients in this group may present symptoms strongly pointing to the urinary tract and yet be sent to the gastroenterologist, the orthopedist, or the exploratory laparotomist for a diagnosis simply because of the negative urinalysis.

Finally, the general practitioner does not need the urologist to aid in making a careful physical examination. In the stricture

patient, as in any other, one may or may not be able to palpate the kidney. In women the right kidney can usually be palpated. The kidney above a stricture is usually, but not always, tender. Even when the kidney cannot be felt, tenderness in the upper flank will usually be elicited.

Palpation of the ureter where it crosses the pelvic brim practically always elicits tenderness in stricture patients. Frequently the patient will refer discomfort so caused to the epigastrium and complain of nausea, or "that old gas pain;" or the discomfort is referred down the ureter to the "ovaries" or to the bladder with a desire to void.

Palpation of the ureter in the broad ligament region usually distinguishes the area of greatest tenderness. The pain may be referred to any portion of the upper ureter, and even to the kidney. The patient often volunteers: "That is the old bladder pressure" or "That is the pressure on the bowel," or "That is my menstrual pain," or "That is the pain I have when using the douche nozzle," or "That is the pain I have with the sexual act." Dyspareunia in the majority of cases is due to the presence of ureteral stricture, and "ovarian neuralgia" is probably more often a ureteral than an ovarian pain. When a patient complains of "falling of the womb" and you find on taking her history and examining her that she is a nullipara, or that she has an outlet in an excellent state of preservation, and apparently normal internal genitalia in normally high position, do not fail to palpate the ureters for the source of her symptoms, for this maneuver often elicits the "falling of the womb" sensation.

Of the many fruitless abdominal operations done because of symptoms due to ureteral stricture, that for supposed appendicitis heads the list. If one simply keeps in mind the usual location of the appendix near the anterior superior iliac spine, and the location of the ureter near the umbilical region, this mistake will not occur so frequently in the future. The ureter, at the pelvic brim crossing, lies over the anterior portion of the sacroiliac joint and one may have difficulty in differentiating by palpation a tender ureter from an arthritis, but we gain additional knowledge by palpation of the joint posteriorly and especially by palpation of the ureter in its juxtavesical portion.

In attempting to differentiate an obscure abdominal complaint by the aid of palpation, one must not lose sight of the fact that ureteritis is of such common incidence that it frequently occurs in association with the various other abdominal and pelvic diseases; and it is the duty of the diagnostician to evaluate the various obscure signs and symptoms and to advise the patient as to the sequence of the proposed lines of treatment.

I have briefly outlined a few of the outstanding features one should bear in mind in attempting to place a helpful diagnostic label on

some of the patients heretofore directed to the wrong specialist or nursed by the general practitioner as neurasthenics. In patients complaining of obscure symptoms referable to a possible lesion in the back, abdomen, or pelvis, an open ear should be kept for any complaint of bladder trouble, an open eye for any suggestion of pathologic findings in the urine, and inquisitive finger tips for any signs of soreness or tenderness along the urinary tract.

Time forbids a full discussion of the many interesting points in differential diagnosis. There is probably no other local disease which gives rise to such protean symptoms as does ureteral stricture. Many of its more general manifestations result, of course, from its effects on the upper urinary tract. Because of its usual location in the pelvis its local discomforts are most often charged to the internal genitalia. From the involvement of the neighboring nerves, we have referred symptoms upward to the flanks, posteriorly to the sacral and sciatic regions, laterally to the hips, and downward to the groin, thighs, legs, and even to the toes. The downward radiations within the pelvis give rise to annoying bladder, uterine and rectal symptoms, and the pains referred to the vagina and perineal regions often lead to misdirected operations.

As a result of the urinary stasis we have all grades of damage to the kidneys, with the resultant local and referred renal pains, and widespread general symptoms such as headache, fever, malaise, thoracic pain, and gastrointestinal symptoms.

The internists who have given attention to this disease report to me their amazement at the number of chronic gastrointestinal complaints which are traceable to defective urinary drainage, and at the satisfactory results obtained from treatment. I cannot emphasize this point better than by quoting from a table in a previous publication[1]:

TABLE I.—ASSOCIATED SYMPTOMS IN URETERAL STRICTURE.

Complaint.	Number of patients.	Relief, partial or, total.	Percentage.
Indigestion	24	17	71
Anorexia	26	20	77
Nausea	56	25	45
Gas	42	26	62
Diarrhea	15	9	60
Rectal pain or pressure	28	19	68
Mucous colitis	15	12	80

Our title calls for a discussion of the pathology and treatment of ureteral stricture, but our space is limited. Those interested in the pathology are referred to a recent publication by Hunner and Wharton,[2] also to the publication by Goldstein and Carson[3]. The chief interest from the pathological viewpoint lies not in a study of the simple inflammatory stricture area of the ureteral wall, but

in a study of the many renal lesions resulting from the stasis of urine caused by the ureteral disease. The more common renal diseases which in large measure may be traced back to the injury caused by ureteral stricture are hydronephrosis (sterile or infected), chronic pyelitis and pyonephrosis, pyelitis of the pregnant and puerperal periods, chronic pyelitis in children, renal and ureteral calculi, the renal inflammatory processes resulting in the so-called essential hematurias, and the various pathological processes which drive to the urologist the patient with congenital malformation of the upper tract. It is probable that many of the chronic nephritides resulting in multiple abortions are secondary to stricture, as are some of the chronic renal processes formerly considered as amenable only to medical methods of treatment.

Inasmuch as the renal injury in the above list of pathological processes arises largely from defective drainage it is a mere truism to state that the first requirement of intelligent treatment is *the establishment of good drainage.* Focal infections are not only responsible for most ureteral strictures, but they sometimes contribute factors of direct injury to the renal substance, thereby furnishing two urgent reasons for the early discovery and eradication of possible foci of infection as one of the primary requisites of treatment in dealing with many of the above renal diseases.

Conclusions. Ureteral stricture is one of the most common lesions of the abdominopelvic cavity. The symptoms due to its presence are most protean in character and lead to more errors in diagnosis and to more ill-directed therapeutics and unnecessary operations than those of any other disease.

The attendant anamnesis and physical findings are such that the general practitioner, if he but have the disease in mind, can usually make the diagnosis with even more certainty than obtains in dealing with cases of chronic appendicitis or chronic cholecystitis.

The chief interest to the pathologist centers in a study of the renal lesions caused by the presence of ureteral stricture.

The treatment is usually nonsurgical and consists in relief of the local symptoms and improvement in the kidney function, by dilatation of the stricture area and restoration of adequate renal drainage. Clinical experience seems to point to distant foci of infection as the most frequent cause of ureteral stricture, and treatment often fails to give permanent relief until the original focus of infection is eradicated.

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DOUBLE TACHYCARDIA.

Coexistent Auricular and Ventricular Tachycardia due to Digitalis.

By Tasker Howard, M.D.,
Brooklyn, N. Y.

Since the return to the use of larger doses of digitalis, for which the careful studies of Eggleston are so much responsible, the usefulness of this drug has been many times enhanced. The popularity of the larger doses, however, has resulted in a very much better opportunity for observing its toxic effects. The danger of overdosage is a very real one, and it is well to be familiar with its toxic manifestations. The occurrence of *A–V* block as a result of digitalis has long been familiar, and was emphasized by Christian[1] in 1915, who reported a series of cases showing such a block with varying ventricular complexes, but not exhibiting tachycardia. In 1918 Vaughan,[2] in reporting 2 cases of ventricular tachycardia, suggested that such a phenomenon might be caused by digitalis, although in his cases this did not seem to be the case. Schwensen,[3] in 1922, reported 2 cases of ventricular tachycardia which were thought to be due to digitalis, and the same year Danielopolu[4] reported 3 cases of paroxysmal tachycardia due to digitalis or strophanthus. These had been observed as early as 1911 and 1913, and the polygraphic tracings which accompany the report leave one in some doubt as to the origin of the tachycardia.

In 1923, Felberbaum[5] reported a case very similar to Schwensen's, and the following year Reid[6] reported 3 cases of ventricular tachycardia due to digitalis. The tracings in the first of his 3 cases seem to show an independent auricular action with *A–V* block.

Luten's[7] studies, published in 1925, include the records of 4 patients with normal cardiac mechanism, in whom large doses of digitalis provoked auricular tachycardia with *A–V* dissociation and independent ventricular rates varying from 90 to 162. Luten drew a parallel between these clinical manifestations, and "the events that occur when the heart of a cat is progressively poisoned by digitalis," as shown by Robinson and Wilson: "First inversion of the *T* wave of the electrocardiogram occurred. After additional amounts of the drug were administered depression of the atrioventricular conduction made its appearance. At about this time there was some slowing of the heart rate, which came on gradually. After still larger amounts there was an increase in the rhythmicity of the auricles and of the ventricles (producing acceleration of both). The ventricular rate soon exceeded that of the auricles thus producing atrioventricular dissociation. At about this stage

idioventricular complexes made their appearance. Independent ventricular rhythm, with abnormal ventricular complexes, developed. This was soon followed by ventricular fibrillation and death."

Another paper of Luten's[7] adds 3 more cases of tachycardia due to digitalis, 1 showing a coexistent auricular and ventricular tachycardia and 2 showing ventricular tachycardia associated with auricular fibrillation. This paper discusses a peculiar type of tachycardia in which alternating types of ventricular complexes occur, corresponding to the cases reported by Schwensen, Felberbaum and one of Reid's cases.

Several of the authors quoted point out the danger of mistaking the rapid, regular, cardiac action of ventricular tachycardia due to digitalis for an auricular flutter, for which more digitalis would be indicated.

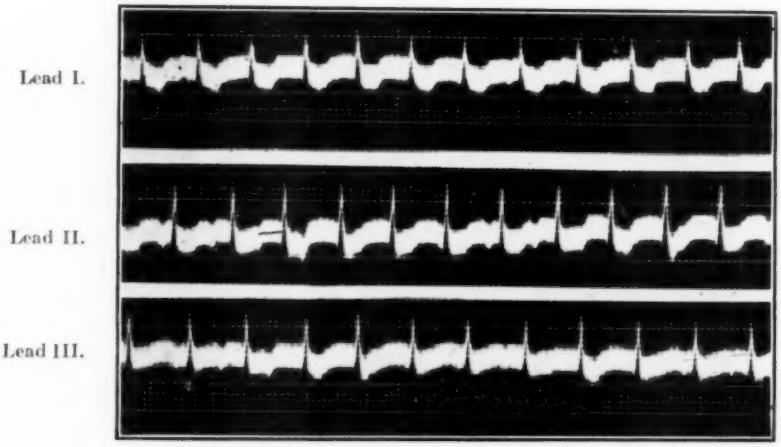
The following case is reported as another instance of the peculiar double tachycardia sometimes caused by digitalis:

Mrs. D. entered the Long Island College Hospital on May 29, on the obstetrical service of Dr. John O. Polak, complaining of orthopnea and weakness. She was eight months pregnant.

She had measles in infancy and rheumatic fever at the age of eight years. At fifteen years she began to notice shortness of breath on exertion, but suffered no serious break in compensation until the present illness. She became pregnant for the first time eight months before admission, and went through the early months of pregnancy without nausea, edema or headache. Four weeks before admission she became very short of breath, and from that time on was incapacitated, dividing her time between the bed and sitting up in a chair. She first noticed edema two weeks before admission and this grew progressively worse. For twenty days before admission she was said to have received 20 minims of digitalis, three times a day, and in the last twenty-four hours was given three doses of strophanthin, gr. $\frac{1}{500}$, hypodermically. The digitalis may have been given as drops rather than minims, which would materially lessen the dose but the total must have been between 40 and 80 cc. She had also been given several doses of morphin for periods of depression, described as sinking spells.

On admission her temperature was 99; pulse, 130; respiration, 28. She was very cyanotic and unable to lie down. She was bled 250 cc. and was given caffein and morphin. The following day she began to vomit and this continued until her death, two days later.

At noon on May 31 the following notes were made: "Pale, little woman propped up in bed, showing moderate cyanosis and a mild degree of dropsy over her sacral region and in the legs. Moist rales at both bases. The heart is enlarged, and presents the typical signs of double mitral disease. The pulse is 168 and is quite



Double tachycardia due to digitalis. Regular inverted *P* waves occurring at the rate of 195. Complete block. Regular ventricular waves of normal contour occurring at the rate of 160.

regular except for recurring waves of somewhat more rapid action, which appear to be of sinus origin. The abdomen shows pregnancy at about the eighth month."

An electrocardiogram was taken an hour later by Dr. C. M. Anderson. Her pulse continued to be very rapid. She grew weaker and more dyspneic, complaining of pain at times in the precordial region. At 9.30 she died. No autopsy was permitted.

The electrocardiogram shows a regular series of inverted *P* waves occurring at the rate of 195. This represents an auricular tachycardia originating in an ectopic focus in the auricle. There is a complete *A–V* block and a perfectly regular series of ventricular beats occurring at the rate of 160 and showing a normal "supraventricular" form. The ventricular tachycardia evidently originates in a focus lying between the *A–V* node and the bifurcation of the bundle.

This combination of auricular tachycardia, *A–V* dissociation, and ventricular tachycardia seems to be a characteristic digitalis effect. Search was made among the published records for similar curves. Gallavardin[8] described such a case in 1920, making no mention of whether or not any drugs of this class had been administered. In the second of Robinson and Herrmann's[9] 4 cases of ventricular tachycardia this combination was noted. This patient probably had a coronary thrombosis, and had been given one dose of strophanthus. The first of the 4 cases of ventricular tachycardia reported by Wolferth and McMillan[10] showed an independent auricular tachycardia, but no mention is made of digitalis. After the paroxysm had subsided a bigeminus was noted. Barker[11] noted periods of ventricular tachycardia during the course of a paroxysm of auricular tachycardia, but no mention is made of digitalis. The same is true of the case reported by Porter,[12] in which the ventricular tachycardia lasted one hundred and fifty-three hours. The curves in this case show *A–V* dissociation with a coexisting auricular tachycardia.

Summary.—1. A brief review of some of the toxic effects of digitalis is presented.

2. Another case is reported in which there was observed auricular tachycardia, *A–V* dissociation and ventricular tachycardia following the administration of large doses of digitalis.

3. Eleven other cases of double tachycardia are collected from the literature. Six of these are known to have received large doses of digitalis. One received but one dose of strophanthin and was probably suffering from coronary thrombosis. The other five may or may not have received drugs of the digitalis class.

Conclusion.—1. The occurrence of A–V dissociation with independent auricular and ventricular tachycardia should arouse the suspicion of overdosage with digitalis.

2. The occurrence of a rapid regular pulse following the administration of drugs of the digitalis class should be studied by the electrocardiograph before proceeding further with digitalis administration.

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SICKLE-CELL ANEMIA; REPORT OF TWO CASES FROM OHIO ILLUSTRATING ITS HEMOLYTIC NATURE.

By H. S. Alden, M.D.,
CINCINNATI, OHIO.

(From the Department of Internal Medicine, University of Cincinnati and the Medical Service of the Cincinnati General Hospital.)

Attention was first called to sickle-cell anemia by Herrick[1] of Chicago, in 1910 when he reported the occurrence of "sickle and bizarre-shaped erythrocytes" in the circulating blood of an East Indian negro. The condition was detected in a routine examination of the blood, and the negro had had no symptoms referable to his anemia. Since this time, there have been reports of 105 cases occurring in different parts of the United States. All these cases have similar symptoms and physical signs and a characteristic blood picture. There have been no reported cases occurring in the white races. Sydenstricker[2] has studied 80 distinct cases and concludes, as does Huck[3] in his studies of 17 cases, that the condition is a familial and hereditary disease of negroes occurring indiscrimi-

nately in both sexes, characterized by the presence of peculiar sickle-shaped erythrocytes in the blood stream, a moderately severe anemia, a varying degree of jaundice, physical and sexual underdevelopment, a general glandular enlargement and, in most cases, ulcer of the legs. Emmel[4] has shown that there are two forms of the disease: (1) Those cases in whom the sickle cells are actually in the circulating blood (the "active sickler"); (2) those in whom the cells become sickle-shaped after standing in a closed chamber for a number of hours (the "latent sickler"). There are all gradations between these types, depending on the severity of the disease.

There have been five necropsies reported on patients with active sickle-cell anemia and the following pathologic conditions were found:

1. A peculiar type of poikilocytosis.
2. A profound anemia.
3. A small, contracted, fibrotic spleen with large numbers of old and recent hemorrhages and evidence of increased blood destruction in and about the Malpighian corpuscles.
4. A bone marrow showing a marked diminution in fat with a large number of sickle- and bizarre-shaped red blood cells, and a rather marked hyperplasia in some cases.

Cases have been reported in various parts of the United States. Two cases have been reported from the midwest and the remaining cases have been reported from Baltimore and in the South.

The following cases are of interest, since they are the first two that have been reported in this locality. They agree in every particular with the cases that have been reported and show the familial incidence of the disease. They show very plainly the many points of similarity of the disease to hemolytic jaundice and how the physical signs may lead one to an erroneous diagnosis of congenital or tertiary syphilis and even an acute appendicitis.

It is through the courtesy of Dr. Roger S. Morris and Dr. A. Graeme Mitchell, on whose services these cases appeared, that I am permitted to make this report.

Case Reports. CASE I.—(Hosp. No. K-3203.) U. H., a negro schoolboy, aged eighteen years, was admitted to the surgical service of the Cincinnati General Hospital, April 22, 1925, with a diagnosis of chronic leg ulcers, probably due to syphilis. His chief complaint was sores on the legs.

Family History. The mother living and well. The father died of a "blood disease," having had ulcers of the legs before death. Two sisters died in infancy. One brother is living and well.

Past History. The patient has always been frail, never able to take part in play with his fellows; he has been under weight and has been troubled with shortness of breath. The patient was born in Georgia, where he lived most of his life. He had pneumonia,

measles and mumps in childhood. He has been unable to play or work to any extent in the past eight years because of leg ulcers. He has suffered at various times with acute epigastric pain and nausea. This soon passed off and he thought nothing of it. He has had no cardiovascular complaints other than his dyspnea on exertion and occasional palpitation. There have been no genito-urinary complaints. He has always had more or less of a greenish-yellow color to his eyes.

Present Illness. The onset was eight years ago, following an abrasion of the left leg which soon enlarged and became an ulcer and persisted in spite of all treatment. An abrasion to the left ankle was soon followed by a similar ulcer.

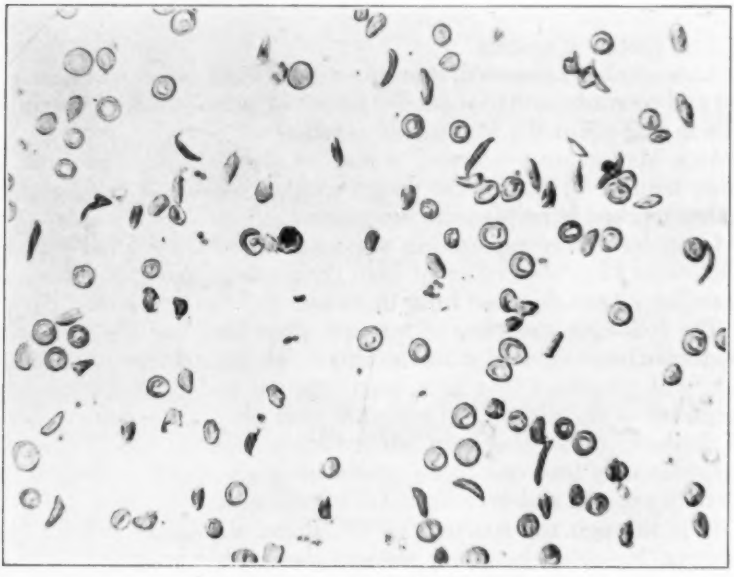

FIG. 1.—Case I. Stained blood smear.

Physical Examination. The patient is a very much underdeveloped negro male of eighteen years, appearing to be about twelve or fourteen years. He is well nourished, however; he does not appear acutely ill. There is a flaring of the lower costal borders with a distended abdomen. There is no pubic or axillary hair. The pulse is of low tension and somewhat frequent; the blood pressure is 98/50. There is a general adenopathy, the glands being hard and shotty. The scleræ show a greenish-yellow color. The pupils are normal. The tongue is pale and moist. There is slight decay of the teeth. The tonsils are small and cryptic. The chest is fairly well developed and symmetrical. Expansion is limited, but equal. The lungs are clear to palpation, percussion and

auscultation. The heart apex is in the fifth space, 10 cm. from the midsternal line. Cardiac dullness extends $11\frac{1}{4}$ cm. to the left, 4.5 cm. to the right in the fourth space. The heart sounds are of fair quality and there is a systolic murmur at the apex, propagated to the left axilla. There is also a systolic murmur at the base, heard best at the pulmonic area. The abdomen is distended, being above the level of the chest, making examination difficult. The liver edge is palpated about 3 cm. below the right costal margin and is slightly tender; the surface seems smooth. The spleen is not palpable. The genitalia are infantile. The muscles of the arms and legs are poorly developed, especially the legs. There is a large superficial ulcer on the anterior aspect of the middle of the left leg, oval in outline, with the long axis parallel to that of the tibia. The edge is rather sharply outlined, slightly undermined, surrounded by deeply pigmented skin which overlies rather dense scar tissue. The base is dirty and covered with unhealthy granulations. Just above the right ankle on the outer side is a similar, though smaller ulcer. The reflexes are normal. Rectal and ophthalmoscopic examinations are normal.

Laboratory Examinations. The white blood cells varied from 15,400 to 9000 and the red blood cells from 1,600,000 to 2,200,000 on discharge; the hemoglobin from 45 to 50 per cent. Differential count showed 23 per cent lymphocytes; 2 per cent large mononuclears and transitionals; 68 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles and 2 per cent basophiles. There was marked; poikilocytosis and anisocytosis; there was 10 per cent of sickle cells. On allowing a sealed wet smear to stand twenty-four hours, there was a very marked increase in the number of sickle cells. Fragility of the red blood cells in hypotonic salt solution was normal. The van den Bergh reaction showed hyperbilirubinemia. The urine was normal, except for a slight increase in urobilin. The gastric contents after an Ewald test meal showed 16 free hydrochloric acid and 43 total acidity. Stool examination on three occasions was normal. Blood Wassermann on three occasions was negative. Roentgen ray examinations of the chest and of the tibiæ were negative.

During the stay in the hospital the patient's temperature fluctuated from normal to 101° F., seldom remaining normal for a whole day at a time. He showed very little reaction to treatment.

Splenectomy was advised, but patient refused to have operation.

The immediate family of the patient were examined. His mother, aged forty years, had no symptoms. Physical examination was essentially negative, except for a slight greenish tinge to the scleræ. The red blood cells were 4,800,000 and white blood cells 6000. The urine was negative. There was a very marked latent sickling of the red blood cells. The brother was normal physically and showed no active or latent sickling of the red blood cells.

CASE II.—(Hosp. No. K-7679.) A. L., a negro boy, aged four years, was first admitted to the Cincinnati General Hospital January 16, 1922, at the age of fourteen months. He was discharged two days later with a diagnosis of rickets and otitis media. The physical examination except for the otitis media and signs of rickets was negative and no note was made of any abnormality in the red blood cells. The blood at this time showed 44,200 white cells, of which 31 per cent were polymorphonuclear leukocytes, 67 per cent lymphocytes, 2 per cent transitional cells.

The patient was admitted the second time in November of 1923 on the contagious service with scarlet fever; was discharged as well, after two months. No abnormality in the blood was noted at this time.

The patient was again admitted on September 22, 1924, complaining of abdominal pain and constipation.

Family History. The mother was living and well; the father was living, but his whereabouts were unknown; two other children were living and well; two children dead, one at eight months, cause unknown, one at fourteen months of chronic bowel trouble. There was no history of miscarriages.

Past History. The patient was a full-term baby with normal delivery, breast-fed for three months, but has always been in poor health. He had had measles, mumps, chicken pox, whooping cough and scarlet fever. The tonsils and adenoids were removed following recovery from the latter.

Present Illness. On the day of admission he had been taken acutely ill with a fever and pain in the abdomen, without any vomiting. He had been constipated for two days.

Physical Examination. The patient is an underdeveloped but fairly well-nourished negro child of three years. His mental capabilities do not seem to have advanced with his age. The abdomen is distended and the costal borders flare. The scleræ have a greenish-yellow tinge. Pupils are normal. The teeth have a chalky appearance. The tonsils are not seen. Respirations are rapid and quick. There is slightly impaired resonance at the base of the right lung but no rales. The cardiac borders are slightly enlarged to the right and a systolic murmur, transmitted equally in all directions, is heard. The abdomen is distended. The liver edge is felt 6 cm. below the costal margin. It is smooth and soft. The spleen is just palpable under the costal margin. There is a slight generalized tenderness of the abdomen.

Laboratory Examinations. The urine was normal. The blood showed 3,200,000 red blood cells; 60 per cent hemoglobin and 14,000 white blood cells. Differential count revealed 71 per cent polymorphonuclear neutrophiles; 11 per cent lymphocytes; 18 per cent large mononuclears and transitionals and a large number of normoblasts. Opinion as to the diagnosis at this time was divided between

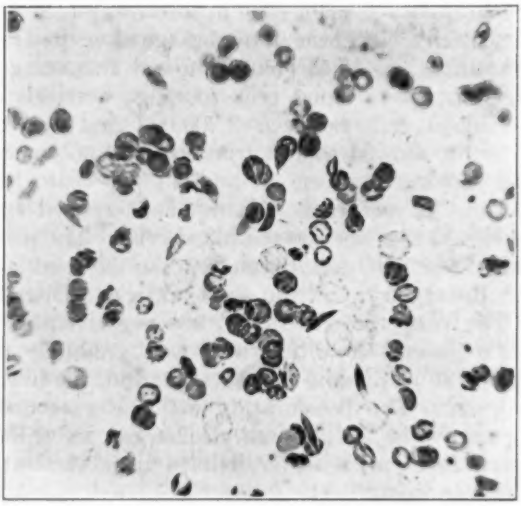

FIG. 2.—Case II. Fresh blood.

FIG. 3.—Case II. Blood after standing thirty-six hours.

a beginning pneumonia and an acute appendicitis. The acute process subsided, however, without operation.

Course in Hospital. During stay in the hospital the temperature remained essentially within the normal range after the first few days. Repeated examinations of the blood showed an average of 60 per cent hemoglobin; white blood cells to range between 20,000 and 14,000; red blood cells between 3,200,000 and 3,750,000. The differential count showed some variations, the polymorphonuclear neutrophiles ranging between 70 and 49 per cent; lymphocytes between 50 and 22 per cent. Normoblasts ranged from 67 per 100 red blood cells to 4 per 100 red blood cells. The platelet count was normal. The van den Bergh reaction showed a hyperbilirubinemia. Roentgen ray of the chest and gastroenteric tract was negative. The Wassermann reaction was negative.

The child's general condition improved gradually, the spleen remained palpable just below the costal margin, the liver decreased somewhat in size. The discoloration of the scleræ remained essentially the same. The patient was discharged December 24 (two months after admission) with no definite diagnosis, but appearing in fairly good condition.

The patient was admitted on October 6, 1925, to the surgical service following a fall in which he suffered injury to the head and right arm. He had been well following the previous admission except for an occasional cold. A diagnosis of acute osteomyelitis was made and the patient was operated on but no pathologic process was found and recovery was uneventful. Physical examination at this time showed practically the same signs as on last admission, the greenish-yellow scleræ, a palpable liver and spleen and the same heart signs. Blood on admission showed 32,000 white blood cells; 60 per cent hemoglobin and 3,500,000 red blood cells; a differential count consisting of 30 per cent polymorphonuclear neutrophiles; 19 per cent lymphocytes and 3.7 per cent transitionals. There was a slight anisocytosis and poikilocytosis. The platelets seemed normal. There were 44 normoblasts to every 100 white blood cells counted. There were 1 to 3 sickle-shaped cells per 100 red blood cells. On allowing a sealed wet smear to stand twenty-four hours there was a marked increase in the number of sickle cells. The van den Bergh reaction suggested increased bilirubinemia of hemolytic origin, but less marked than on the previous admission. Fragility of the red blood cells was normal. The urine was normal except for a slight increase in the urobilin content. The patient improved slightly under rest and iron tonics but an acceptable donor for transfusion could not be obtained and splenectomy was thought inadvisable because of the anemia. Patient was discharged on December 14 as improved, with a diagnosis of sickle-cell anemia.

The mother of this patient was examined. She had no symptoms. She was undernourished and underdeveloped. Physical examination was essentially negative except for a slight greenish tinge to the scleræ. Red blood cells were 3,800,000; white blood cells were 7000. There was a marked latent sickling of the red blood cells. Urinalysis was negative.

Comment. Case I shows plainly how the sickle-cell anemia may be confused with tertiary syphilis. For three months the patient's leg ulcers were considered syphilitic in origin. In Case II the pain in the abdomen and distention coming on suddenly was in all probability due to a splenic hemorrhage, yet it was thought to be an acute appendicitis at the time.

The treatment of sickle-cell anemia is very unsatisfactory. The general supportive measures, overfeeding, iron, and with rest in bed give only temporary relief. The good from transfusion is only short-lived. Splenectomy has been suggested but never attempted. In view of the fact that the disease is so similar to hemolytic jaundice, in which splenectomy is curative, and that all or most of the red-cell destruction apparently takes place in the spleen, it seems that splenectomy should be tried. The prognosis is bad. The course of the disease is gradually a downward one, the patients rarely living beyond thirty years of age.

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ESSENTIAL HEMATURIA AND ITS POSSIBLE RELATIONSHIP TO PURPURA HEMORRHAGICA.

By H. Milton Conner, M.D.,

and

Hermon C. Bumpus, Jr., M.D.,

division of medicine, mayo clinic, rochester, minn.

When a careful cystoscopic examination demonstrates hemorrhagic urine coming from one or both kidneys which give normal functional tests, and the pyelograms are negative, a diagnosis of essential hematuria is warranted. To assert that such a diagnosis means that an early neoplasm, nonopaque calculi or an obscure infection has been overlooked would seem to discredit the perfection of modern urologic technique or the capability of the examiner. That such oversights are the exception rather than the rule is the experience of every urologist who has followed a series of cases of essential hematuria over a period of years. Neoplasm does not eventuate nor are stones passed, nor does tuberculosis or other infection usually appear. Good health is usually maintained and recurrence seldom follows proper treatment.

It is unfortunate that a diagnosis of essential hematuria should be interpreted by some as evidence that a gross lesion of the urinary tract surely has been overlooked; it is as deplorable as it is inevitable that this desire to limit the etiology of this disease to a narrow field should tend to discourage search for some more remote and more obscure cause.

Several years ago Quinby[1] studied 2 cases of essential hematuria in which nephrectomy had been performed. He found that the hemorrhage was from the pelvis and the tips of the pyramids. In each instance hemorrhage occurred within the peripelvic tissues, often appearing just beneath the epithelium, where, for considerable distances, the epithelium had been elevated by a layer of extravasated blood. In 1 case there was no evidence of inflammatory reaction in the tissues of the pelvis or around the bloodvessels. The hemorrhages were represented by extravasations of red blood cells from thin-walled dilated capillaries and veins. Just beneath the epithelium of the pelvis unruptured, large, thin-walled vascular channels were seen, evidently considerably distended. Even larger arteries showed extravasated blood external to the adventitia. The vascular channels between the collecting tubules of the pyramids, especially those nearer the apex, were very wide, often irregular and tortuous, giving the appearance of vascular sinuses rather than of veins or capillaries. These sinuses were distended with blood. Although no organisms could be demonstrated in either

case, in the second there was more suggestion of an infectious cause, there being a distinct inflammatory reaction and evidence of vascular injury.

Believing from these findings that an obscure focus might be the cause of these localized lesions in the kidney, we injected a considerable number of laboratory animals with cultures from foci of infection in 9 patients having essential hematuria. In none of these animals could we demonstrate any renal lesions, although Meisser, with whom we were carrying on this laboratory study, was finding positive results in more than 80 per cent of animals similarly injected with cultures from patients suffering with pyelonephritis and elusive ulcer of the bladder of Hunner.

Because of the fact that bleeding elsewhere, especially from the nose, skin, mucous membrane of gums and mouth, or in the subcutaneous tissues, alone or in combination, is seen as a result of a deficiency of some blood element necessary to the maintenance of the blood in the vessels, it seemed possible that some deficiency of elements necessary for the coagulation of blood might explain certain cases of essential hematuria.

Instances of hematuria are not unusual in cases of purpura of various forms and cases of hemophilia. Cases of purpura of the urinary tract, with cystoscopic finding of purpuric areas in the bladder, without hemorrhage elsewhere, have been described by Blum[2] and Praetorius.[3] Yet we find no suggestion in the literature that cases of bleeding from the kidney for long periods or at long intervals may be due to a deficiency in some of the coagulation elements of the blood. The possibility that such might be the case with essential hematuria was enhanced by the observation by one of us (Conner) of several cases of menorrhagia without local explanation, which we believed to be due to a deficiency in coagulation factors. It is possible that some cases of local hemorrhage elsewhere, in the stomach, intestine, eye and so forth, may be explained on the same grounds.

If, besides a deficiency in some of the coagulation factors, there is a local predisposing cause, such as unusual vascularity of the mucous membrane or an area of localized infection, the possibility of bleeding is greatly increased. That lavage of the renal pelvis with a styptic solution, such as silver nitrate, will frequenty stop such bleeding would suggest such a localized cause.

In searching for some factor concerned in the coagulation mechanism of the blood we paid particular attention to the blood platelets, coagulation time and bleeding time. The calcium coagulation time and the prothrombin time were also estimated in nearly all cases, and the possibility of bleeding elsewhere was carefully investigated.

Thirty-three unselected cases were observed. Most of them were seen between December, 1923, and September, 1925. In 22 the diagnosis of essential hematuria was unquestioned; in 11

others a diagnosis of probable essential hematuria was made. A study was made of age, sex, lapse of time since the first appearance of hematuria, family history of bleeding, and personal history of bleeding from the gums, epistaxis, hemoptysis, hematemesis, melena, menorrhagia, purpuric spots and "easy bruising." At the examination particular attention was paid to the presence of petechiæ, purpuric spots, hemorrhagic areas of the gums and mouth, to the tourniquet test and palpability of the spleen.

Cases of Essential Hematuria (Table I). The oldest of the 22 patients was sixty-seven years and the youngest nineteen years; the average age was forty-two and a half years. There were 15 males and 7 females. The duration of the symptoms was from two days to twenty years; in 1 case the duration was not recorded, and the average duration for the other 21 cases was five years and forty-one weeks. There was a history in 5 cases of other members of the family having suffered from hemorrhage, no such history in 11 and no record in 6. The mother had had epistaxis in 1 case, the father intestinal hemorrhage in 1, a brother hematuria in 1, the mother hemoptysis in 1 and a son epistaxis in 1. Personal history of bleeding from the gums was positive in 2 cases, negative in 16 cases and there was no record in 4. Epistaxis had occurred in 5 cases, in 14 it had not and in 3 there was no record. There was no history of hemoptysis in 18 cases and there was no record in 4. In 19 cases hematemesis had not occurred, and there was no statement regarding it in 3. In 19 cases melena was not admitted and there was no record in 3. In 2 of the 7 female cases menorrhagia had occurred; in 5 it had not. In 18 cases the existence of purpuric areas was denied; in 1 the patient stated that they had occurred, and there was no statement regarding it in 3 cases. There was a history of "easy bruising" with resultant "black-and-blue" areas in 2 cases; it had not occurred in 14 cases and in 6 there was no record. There was a history of gross hematuria in all but 1 case.

On examination there were no petechial areas nor purpuric spots noted, and no hemorrhagic areas elsewhere. The tourniquet test was rated in 1 case as Grade 1−, on a scale of 1 to 4; in 5 cases as Grade 1, in 2 as Grade 1+, in 3 as Grade 2, in 1 simply positive and in 7 negative. In 3 cases no statement was recorded.* The spleen was not felt in any instance; there was a specific note of inability to palpate the spleen in 7 cases and no specific mention made of the spleen in the other cases.

* The tourniquet test is made by applying the arm band of the sphygmomanometer above the elbow for exactly three minutes at a pressure midway between the systolic and the diastolic pressures, usually about 100. The appearance of petechial areas below the band is interpreted as a positive test. This test is one of importance in the diagnosis of purpura hemorrhagica. The extent and intensity of the subcutaneous hemorrhage indicate the degree of positiveness of the test.

The number of erythrocytes varied from 3,720,000 to 4,990,000 per c.mm., the average being 4,344,000. The hemoglobin varied from 60 to 88 per cent, and averaged 72 per cent; it was measured with the Dare instrument, which is somewhat too low in the higher readings. The number of leukocytes varied from 4600 to 12,000 per c.mm., averaging 7800. The platelet count varied from 74,000 to 272,000 per c.mm., averaging 141,000; the lowest average platelet count for the individual patient was 96,000 and the highest 202,000, the normal platelet count being between 200,000 and 250,000. In 1 case the platelets averaged below 100,000; in 5 cases, from 100,000 to 125,000; in 6 cases between 125,000 and 150,000; in 8 cases between 150,000 and 175,000; in 2 cases, more than 200,000. In 6 cases one count was below 100,000; in 2 cases two or more counts were below 100,000. It is interesting that in all except 1 case in which any degree of positiveness of the tourniquet test was shown the platelet count was more or less lowered. Conversely, in most cases in which a lowered platelet count was shown there was some degree of positiveness of the tourniquet test. The coagulation time by the Boggs method varied from three to eight and a half minutes, averaging five and three-tenths minutes. The normal time is from three to five minutes. The bleeding time varied from one to three and a half minutes, with an average of one and four-fifths minutes. The normal bleeding time is from one to one and a half minutes. The coagulation time by the Lee method varied from five and a half to sixteen minutes, averaging nine and two-fifths minutes. The normal time is from eight to eleven minutes. In no case was there sufficient change in the coagulation time by the addition of calcium to justify the assumption that there was a deficiency of calcium in the blood. In no case was the prothrombin time sufficiently prolonged to justify the assumption that there was a deficiency of prothrombin in the blood. In 1 case the prothrombin time on one examination was sixteen minutes with the optimal amount of calcium, but on another examination the time was twelve minutes; in 1 case the prothrombin time was twenty-six minutes on one examination and later only eleven minutes. In both of these second tests the results were within normal limits. The clot-retraction time was normal in all except 1 of the 6 cases in which the test was done; in this 1 case retraction was complete in two hours instead of one hour, as is normal. The Wassermann reaction was negative in the 18 cases in which the test was made. There was gross hematuria at the time of examination in 9 cases, and no hematuria at the time of examination in 2 cases. Infection of the teeth was present in 5 cases as Grade 1, in 5 cases as Grade 2 and in 2 cases as Grade 3. There was evidence of chronic tonsillitis in 9 cases, and the tonsils had already been removed in 3 cases; no mention was made of the tonsils in 5 cases.

TABLE I.—ESSENTIAL HEMATURIA.

Case.	Age, years and sex.	Duration of illness.	History.										Examination.																		
			Family history of bleeding.	History of bleeding gums.	Epistaxis.	Menorrhagia.	Hemoptysis.	Hematemesis.	Melena.	History of gross hematuria.	Purpura.	Easily bruised.	Petechiæ.	Purpuric spots.	Hemorrhagic areas elsewhere.	Tourniquet test, grade.	Palpable spleen.	Erythrocytes, millions per c.mm.	Hemoglobin, per cent.	Leukocytes, thousands per c.mm.	Platelet counts, thousands per c.mm.	Average platelet count, thousands per c.mm.	Coagulation time (Boggs), minutes.	Coagulation time (Lee), minutes.	Bleeding time, minutes.	Calcium time, minutes.	Prothrombin time with optimal calcium, minutes.	Clot retraction in one hour.	Hours in which clot retraction is complete.	Wassermann reaction.	Teeth, periapical infection.	Tonsilitis.	Hematuria, grade.
1	45 F.	8 yrs.	–	0	0	1	0	0	0	+	+	+	0	0	0	1	–	4.63	71	8.0	122 130	127	4.5	9.0	2.0	9.0	10	0	2.0	0	2	+	0
2	35 M.	5 yrs.	–	–	–	..	–	–	–	+	–	–	0	0	0	0	–	4.59	70	7.5	130 180	149	5.0	16.0	1.5	11.0	10	–	–	0	2	*	5
3	54 M.	3 wks.	0	–	–	..	–	0	0	+	–	–	0	0	0	+	0	4.36	70	6.8 12.0 5.9	174 94 162	 137	.. .. 7.3	12.0 13.0 6.5	1.0 .. 3.0	14.0 10.0 9.0	10	–	–	0	1	+	3
4	46 F.	20 yrs.	0	0	0	0	–	–	–	+	0	0	0	0	0	0	–	4.26	70	7.9 6.8	120 130	.. 134	.. 4.0	15.0 9.5	.. 2.0	9.0 9.5	10	–	–	0	3		
5	55 F.	20 yrs.	–	–	0	+	0	0	0	+	0	0	0	0	0	0	–	4.46	71	7.6	138 156	.. 169	4.0 7.0	.. 7.0	2.0 3.5	14.0	16	–	–	0	3	0	3
6†	52 M.	12 yrs.	0	0	0	..	0	0	0	+	0	0	0	0	0	2	0	3.86 4.31	65 74	6.5 4.6	182 80	— 100	5.5 4.5	.. 6.5	1.5 1.5	.. 4.5	12 10	–	–	0	3	0	3
7	38 M.	17 yrs.	0	0	1	..	0	0	0	+	0	–	0	0	0	1	–	4.57 4.21	72 70	9.2 7.3	94 126 106 122	100 ..	8.5 7.5	12.0 7.0	6.5 2.0	20.0 8.5	11 26	–	–	0	3	*	4
8	21 M.	1 yr.	0	0	1	..	0	0	0	+	0	0	0	0	0	0	0	4.48	80	11.0	74 272	.. ..	6.0 4.0	.. 12.0	2.0 3.5	5.5 15.0	11	–	–	0	–	*	4
9	26 M.	3 mos.	Mother, epistaxis	0	0	..	0	0	0	+	0	+	0	0	0	1	–	4.37	74	7.6	146 172 168	162	4.0	8.0	3.0	9.0	13	–	–	–	2	+	5

10	48 F.	12 wks.	0	0	0	0	0	0	0	+	0	–	0	0	0	1+	–	4.57 3.95	75 67	7.8 ..	162 226 174 106 116	157 ..	3.5 5.0	5.5 ..	1.5 1.5	5.0	–	–	–	0	1	0	5
11	28 F.	7 mos.	Father, intestinal hemorrhage	1	0	0	0	0	0	+	0	–	0	0	0	1	–	4.83	73	7.4	146 140 122	136	5.0	10.0	1.0	10.0	10	–	–	0	0	–	4
12	19 F.	2 yrs.	–	0	0	0	0	0	0	+	0	0	0	0	0	1	–	4.04	65	8.8	130 172 166	156	6.0 4.0 6.0	5.0	1.5 2.0 2.0	7.0	10	Marked	1.0	0	0	–	0
13	36 M.	4 yrs.	Brother, hematuria	0	0	..	0	0	0	+	0	0	0	0	0	1 –	0	4.31	73	5.4	136 98 106	113	6.0 3.0 4.0	7.0	1.5 1.5 2.0	7.0	11	2 hrs.; marked	2.5	0	2	+	5
14	34 M.	8 yrs.	0	1	0	..	0	0	0	+	0	0	0	0	0	1+	–	4.55	78	7.5	94 206 78 180 228 166	159	4.0 4.0 7.0 6.0 5.5 6.0	8.0 7.0	1.0 3.0 2.0 1.0 2.0 1.0	10.0	10	2 hrs.; marked	3.0	0	2	+	5
15	23 M.	10 yrs.	Mother; hemoptysis	0	3	..	0	0	0	+	0	0	0	0	0	–	–	4.99 4.54	76 88	9.4 7.7	112 80	96 ..	6.0 3.5	11.5 ..	1.5 2.0	10.0	–	–	–	0	1	+	4
16	57 M.	9 yrs.	Son, epistaxis	0	0	..	0	0	0	+	0	0	0	0	0	0	0	4.41 4.31	71 60	6.9 8.0	200 160 110	156	5.0 7.0 6.0	7.0	2.0 1.5 1.5	7.0	10	Marked	1.5	0	?	–	5
17	60 M.	2 wks.	0	0	0	..	0	0	0	+	0	0	0	0	0	2	0	4.09	72	6.6	190 148 268	202	5.0	6.0	1.5	4.0	10	–	–	0	*	+	1
18	67 M.	3 wks.	–	0	3	..	0	0	0	+	0	0	0	0	0	2	0	4.14 4.09	70 71	8.3	90 100 156	115	4.5 5.0 4.5	11.0	2.0 2.0 2.0	7.5	10	Complete	1.0	0	–	–	5
19	46 F.	4 yrs.	0	0	0	0	0	0	0	+	0	0	0	0	0	0	–	4.00 3.72	72 60	10.1	132 132 188	151	7.0	7.0	1.5	8.0	11	–	–	0	0	0	5
20	45 M.	?	0	0	2	..	0	0	0	0	0	0	0	0	0	–	–	4.53 1.52	71 77 ..	4.8 .. 3.0	94 74 152 100 98	103	6.0 5.0 5.5 5.5	8.0 12.0	1.5 1.5 1.5 2.5 1.5	9.0 11.0	12	–	–	0	0	–	3
21	50 M.	4 mos.	0	0	0	..	0	0	0	+	0	0	0	0	0	0	–	4.60 4.32	75 70	8.2 5.7	128 190	159 ..	3.5 6.5 6.5	9.0 10.0 ..	1.5 1.5 3.0	12.0 15.0	10 10	–	–	0	1	0	3
22	41 M.	6 wks.	–	–	–	..	–	–	–	+	–	–	–	–	–	–	–	4.26	70	12.0	130	..	8.0	8.5	1.0	8.0	11	–	–	0	1	0	4

* Tonsils had been removed elsewhere.

†Patient would not consent to cystoscopic examination.

TABLE II.—POSSIBLE ESSENTIAL HEMATURIA.

| Case. | Age, years, and sex. | Duration of illness. | History. | | | | | | | | | | Examination. | | | | | | | | | |

Probable Essential Hematuria. There were 11 cases in this group. Reference can be made to Table II for details of clinical and laboratory evidence. These cases did not differ much in important details from the group of definite cases. The average age was approximately the same. The platelet count averaged 131,000, about half the normal.

Discussion. Of the 22 cases of unquestionable essential hematuria, the platelet count was less than 150,000 per c.mm. in 12 cases (54.5 per cent); in the group of 11 cases of probable essential hematuria the average platelet count was below 150,000 in 10 cases (91 per cent). The platelet averages of 141,000 and 131,000 in the two groups are only a little in excess of one-half the normal. The decreased number of platelets, together with the positive tourniquet test, in a rather high percentage of those cases in which it was made suggests that it is possible that we are dealing with a group of cases in which bleeding occurs from a deficiency in blood platelets, as it does in cases of purpura hemorrhagica or thrombocytopenic purpura. In 2 cases in the group of unquestionable essential hematuria there was a history of easy bruising and in 1 of these a few purpuric areas had been present. In 1 case in the group of probable essential hematuria there was a history of easy bruising and there had been a few purpuric areas at times before the examination at the clinic. Symptoms and laboratory evidence of purpura hemorrhagica appeared later. No bleeding from any source has occurred since the removal of the spleen in April, 1925, when cirrhosis of the liver with moderate ascites was also found. Therefore, this case does not entirely conform to the group of true purpura hemorrhagica. Hematuria had been present for two and a quarter years before the appearance of purpura. It seems rather likely, even though the hemorrhage may be primarily due to the deficiency in platelets, that a local predisposing cause also exists. The response to local applications of silver nitrate is suggestive of a local predisposing cause, while the response to the use of the serum of the horse and of man and to injections of autogenous whole blood is suggestive of its origin in coagulation deficiency or a deficiency in blood platelets.

As normal controls, estimations of the number of platelets and of the coagulation and bleeding times, were made on 7 healthy men. An average platelet count of 198,000 per c.mm., Bogg's coagulation time of six and a half minutes and the bleeding time of two and one-tenth minutes were found. In the 12 cases of definite purpura hemorrhagica in which operation was performed at the Mayo Clinic in the last three years, 9 of which have already been reported by Giffin and Holloway,[4] the platelet count previous to operation averaged 85,000. In cases in which there had been recent hemorrhage, not accompanied by any evidence of purpura or by essential hematuria, the average platelet count was 231,000.

† Pyorrhea.
* Black-and-blue.
0, negative; +, positive; — indicates no test made.

The foregoing is presented in the hope that it will incite further investigation of these cases from the standpoint of the blood. There is not enough evidence at hand to prove that essential hematuria is ever localized purpura hemorrhagica or due to a deficiency of blood platelets, but the evidence is rather suggestive that this is true in some cases.

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THE RELATIONSHIP OF OBESITY TO CARBOHYDRATE METABOLISM.

By Henry J. John, M.D.,
CLEVELAND CLINIC, CLEVELAND, OHIO.

The relation of body weight to height, age and sex and the interrelation of these with reference to the well-being of the individual has held the interest of the medical profession ever since the time of Lavoisier and many researches in this field have been made by French, German, English and American investigators. It is well recognized that a normal individual tends to maintain a certain average body weight, this average being maintained by a regular intake of water and food. In the processes of metabolism the ingested food is transformed into heat energy and is in part eliminated, the remainder being stored in the tissues in the form of combustible materials such as proteins, carbohydrates, and fats, which are readily available for the supply of energy when the food intake is not sufficient to supply the organic need. Thus, when the supply of food is in excess of the metabolic needs or when it is stored at the expense of the energy demand, this excess is stored chiefly in the form of fat and in consequence the body weight increases; on the other hand, when the supply of food is inadequate the materials previously stored are used up and there results a decrease in the body weight which, if carried far enough, produces emaciation.

In considering the significance of an increase in the body weight, three types of obesity have to be considered:

1. The *exogenous type* which is most frequently encountered, in which overweight is due to an oversupply of food. This type of

obesity may be identified by the basal metabolic rate, which in these individuals, according to Means,[1] is always within the normal limits.

2. The *endogenous type*, in which there is usually some endocrine disturbance. This group includes cases of thyroid deficiency, imbalance of gonad hormones, and of hypophyseal disturbance, each of which is characterized by a low basal metabolic rate. It is interesting in this connection to note that, as has been stated by du Bray,[2] the overweight in myxedema is less constant and striking than the undernutrition seen in hyperthyroidism. Following thyroidectomy, an increase in the body weight is often noted. Overweight due to an imbalance of the gonad secretions is quite commonly encountered in women after the onset of the menopause, and is also seen in animals and in man after castration. Overweight due to a hypophyseal disturbance, known as Fröhlich's syndrome, is less well understood, on account of the complex structure of the hypophysis cerebri. Investigations regarding the functions of the different portions of this gland are being carried on all over the world, and some day will aid in the interpretation of obesity due to this cause. Estimations of the basal metabolism are of great value in the study of this entire group of cases, in which, as stated above, the metabolic rate is below normal; and organotherapy, as one would suppose, is the most effective form of treatment.

3. The *constitutional type*, which has been thus tentatively designated by Strouse,[3] and his coworkers. Individuals with this type of obesity are unable to lose weight even when a very low caloric diet of from 600 to 1000 calories per day is maintained for long periods of time. The basal metabolism in cases of this type is within the normal limits, and it would appear, therefore, that the metabolism of individuals in this group does not depend either on the amount or kind of food or on any endocrine disturbance, this fact making possible the differentiation of obesity of this type from the two types described above.

The relation of overweight to diabetes has been strongly emphasized in this country by Allen and Joslin. Paullin and Sauls[4] have recently reported a series of 26 cases of obesity in relation to their carbohydrate tolerance. The ages of these patients ranged from 10 to 80; the overweight from 10 to 82.1 per cent. Unfortunately, the glycemic curves were carried for only two hours after the injection of glucose so that the interpretation of borderline cases is difficult, yet the results secured by these investigators are interesting, since in 57.6 per cent of this group the glucose tolerance was abnormal. "We feel quite strongly that the results are significant and that by a study of the glucose tolerance test, even in so small a number of patients, we have detected at least five prediabetics. Two of the five have definitely developed diabetes." It is obvious that when a clinician is confronted with an obese patient he should

TABLE I.—SUMMARY OF 12 CASES OF OBESITY.

Case number.	Age.	Sex.	Per cent overweight.	Glycosuria.	Fasting blood sugar, mg. per 100 cc.	Basal metabolic rate.	Glucose tolerance.	Complaint.	Diagnosis.
1 . . .	20	F.	115	Negative	109	+ 9	Normal	Obesity	Endogenous obesity
2 . . .	14	F.	52	Negative	112		Normal	Obesity; stiff neck	Endogenous obesity; fibrosis of sternocleidomastoid
3 . . .	19	F.	40	Negative	94	− 5 2	Normal	Boils; frequency of urination	Endogenous obesity
4 . . .	32	F.	32	Negative	97		Normal	Obesity	Endogenous obesity?
5 . . .	40	M.	80	Negative	95	+28	Normal	Slow pulse; high blood pressure	Exogenous obesity; hypertension; chronic nephritis
6 . . .	48	F.	29	+++	105		Diabetic	Pain in right hypochondrium	Diabetic obesity; chronic cholecystitis; diabetes mellitus
7 . . .	36	M.	35	+	92		Normal	Headaches	Endogenous obesity; hypertension; chronic nephritis; nondiabetic glycosuria
8 . . .	28	F.	86	Negative	95	+12	Normal	Shortness of breath	Endogenous obesity; hypertension; chronic nephritis
9 . . .	19	F.	64	Negative	107	− 8	Diabetic	Nervousness, stomach trouble	Endogenous obesity; dystrophia adiposogenitalis
10 . . .	36	F.	48	Negative	111		Prediabetic	Gas on stomach	Endogenous obesity
11 . . .	27	F.	61	Negative	111	+25	Diabetic	Amenorrhea	Endogenous obesity; diabetes mellitus
12 . . .	39	M.		+++	213		Diabetic	Dizzy spells; headaches	Endogenous obesity; diabetes mellitus

feel the responsibility of determining whether or not diabetes is present. The loss of weight which is generally considered to be a characteristic of diabetes is a phenomenon which develops later in the disease and may properly be called an "end stage." It is in connection with this problem of differentiating potential from true diabetes in obese patients that I have gathered the data regarding 12 cases of obesity in which a glucose tolerance test was made. Sufficient evidence on which to base conclusions regarding the relationship of obesity to diabetes would require the accumulated data in a series of at least 1000 cases, but this small group of cases may offer at least an indication as to the significance of obesity in its relation to carbohydrate metabolism and consequently to diabetes.

Case Reports. CASE I.—(138,940.) The patient was a woman, aged twenty years, who came to the Clinic because of obesity, her weight at the time of the first visit being 269 pounds. The personal and family history contained no significant data. There was no familial history of obesity nor was the patient a heavy eater. The patient's height was 5 feet 4 inches, so that her normal weight would have been 125 pounds. She was, therefore, 115 per cent overweight. Her blood pressure was 150 systolic, 80 diastolic.

The physical examination gave no significant information except for the obesity. A Roentgen ray examination of the skull showed that the sella turcica was normal in size. The urine showed a trace of albumin but was otherwise normal. Blood examination: White blood cells, 7000; red blood cells, 4,470,000; hemoglobin, 85 per cent. Blood chemistry: Sugar, 109 mg.; urea, 18 mg.; uric acid, 2.9 mg.; creatinin, 1.5 mg. and plasma chlorids, 605 mg., per 100 cc. of blood (all fasting values). The blood Wassermann was negative. The basal metabolic rate was +9.

The glucose tolerance curve in this case is shown in Chart I (I).

In this case the presence of some abnormal condition of the hypopituitary gland was suspected for although the roentgenogram gives no evidence of any enlargement of the pituitary body, it naturally could not demonstrate the presence of any functional changes within the gland. That such changes might well have been present is suggested by the glucose tolerance curve, which is typical of that obtained in cases of hypopituitarism, that is, it shows the carbohydrate tolerance to be above the normal.

CASE II (131,166).—This patient was a very obese girl, aged fourteen years, apparently in good general health, who sought medical consultation on account of stiffness of the right sternocleidomastoid muscle. The family history gave no significant information. She had had whooping cough, chickenpox, influenza, tonsillitis and three attacks of measles. The sternocleidomastoid muscle had begun to be stiff two years before. At the time of her first visit to the Clinic, the patient weighed 173 pounds. Her height was 5 feet 5 inches, so that her normal weight would have been 114 pounds. Thus she was 52 per cent overweight.

There was no glycosuria and the fasting blood chemistry gave the following information: Sugar, 112 mg.; urea, 24 mg.; uric acid, 2.7 mg.; creatinin, 1 mg.; nonprotein nitrogen, 27.8 mg.; plasma chlorids, 615 mg. per 100 cc. of blood. The blood Wassermann was negative.

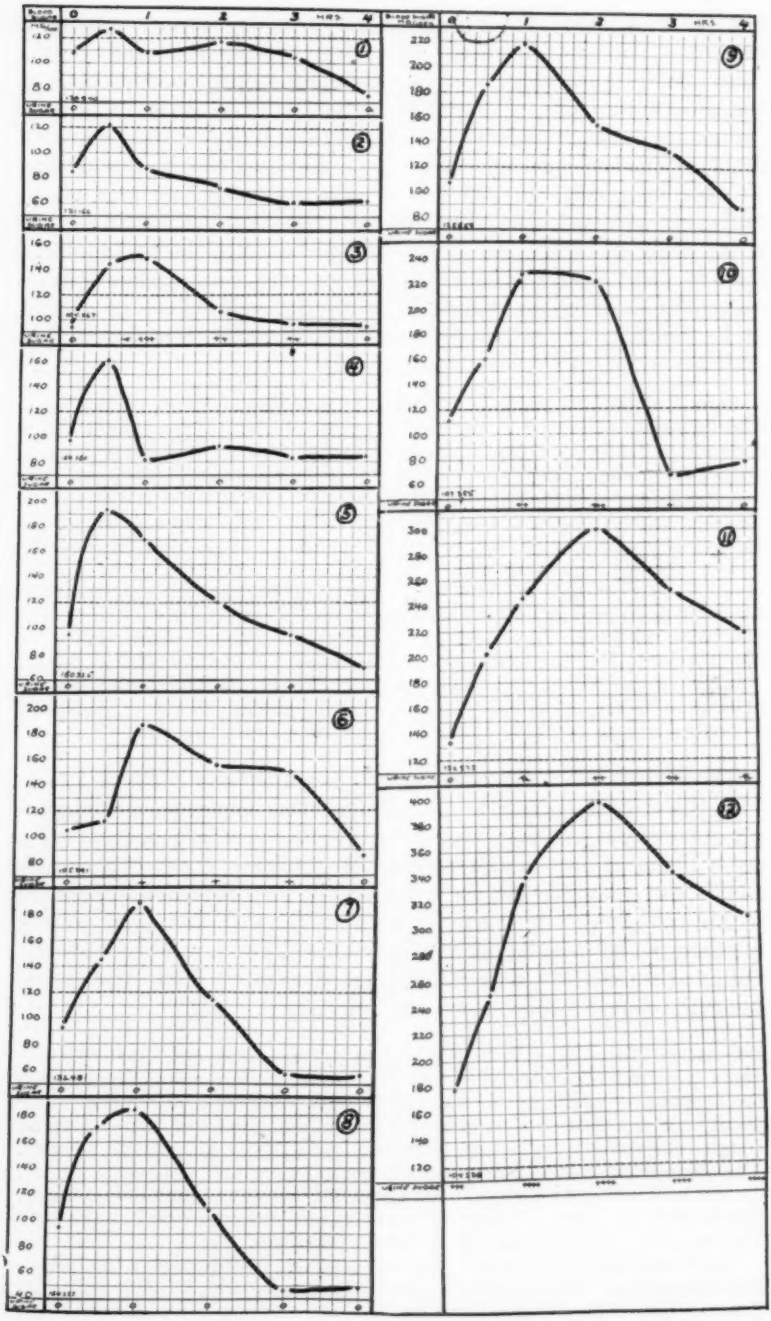

CHART I.—Glucose-tolerance curves of each of 12 cases of obesity described in text. (In each case the first reading was taken.)

A glucose tolerance test gave the normal curve shown in Chart I (II).

Case III (104,267).—The patient, was a young woman, aged nineteen years, weighing 185.9 pounds. Her mother had diabetes, but otherwise the family history gave no significant information. The patient sought medical advice because of frequent attacks of boils during the preceding two years. She had had none of the usual diseases of childhood but had had two attacks of pneumonia during the two years before this consultation. She said that she had had occasional attacks of influenza and of tonsillitis, although a tonsillectomy and adenoidectomy had been performed six years before. Her menses were irregular, often being absent for periods of six or seven months. Her specific complaints were of boils and of frequency of urination. She had been eating very sparingly of carbohydrates, having entirely eliminated pastry and potatoes from her diet.

Physical examination disclosed a small adenoma in the right lobe of the thyroid. Otherwise no abnormalities were found excepting the excessive weight. The height of the patient was 5 feet 7 inches so that she was 40 per cent overweight. The blood pressure was 120 systolic and 60 diastolic, urine, normal. Blood examination: White blood cells 8,800; red blood cells, 4,670,000; hemoglobin, 70 per cent. Blood chemistry: Fasting blood sugar, 94 mg.; urea, 18.7 mg.; plasma chlorides 598 mg., per 100 cc. of blood. The blood Wassermann was negative. Basal metabolic rate was minus 5.2.

A glucose tolerance test gave the curve shown in Chart I (III). This is a normal tolerance curve associated with a very low renal threshold for sugar. Because of the low threshold glycosuria could easily appear during the postprandial period in such a case, and this, together with the history of boils and the obesity, would strongly suggest the presence of a diabetic condition. Yet the glucose tolerance curve shows quite clearly that the obesity in this case is not associated with diabetes, but that it is of either the exogenous or the endocrine type.

Case IV (154,280).—This patient, a woman, aged thirty-two years, weighing 160 pounds, came to the Clinic for physical examination chiefly on account of her obesity. Her father and mother had both died of diabetes. She herself had had none of the diseases of childhood and no illnesses later in life. She was 5 feet 1 inch in height, so that she was 32 per cent above her normal weight which would have been 121 pounds. Physical examination disclosed nothing abnormal. The blood pressure was 120 systolic, 80 diastolic. Urine, normal. Blood examination: White blood cells, 9000; red blood cells, 4,560,000; hemoglobin, 80 per cent. The blood Wassermann was negative. Blood chemistry: Sugar 97 mg.; urea, 21 mg.; uric acid, 2.5 mg.; creatinin, 0.9 mg.; nonprotein nitrogen, 30.4 mg.; plasma chlorids 595 mg., per 100 cc. of blood.

The glucose tolerance curve, Chart I (IV), shows a normal tolerance for carbohydrates, thus ruling out the possibility that the overweight in this case was due to a diabetic condition.

Case V (160,325).—This patient, a man, aged forty years, weighing 270 pounds, came to the Clinic because of a slow pulse rate and high blood pressure. The family history gave no significant information. Of the

childhood diseases, he had had measles and diphtheria and later in life he had had tonsillitis and influenza. A tonsillectomy had been performed twenty years before. He was a heavy smoker, having used from 50 to 100 cigarettes a day, although at the time of the consultation he had reduced this daily consumption to five or six. He said that a year before this consultation he had developed a pulse rate of 120 and had begun to gain weight rapidly. Eleven months before he had begun to lose weight, his pulse rate had begun to drop and his blood pressure to rise. The pulse rate had dropped to between 50 and 60 and he had been having a "feeling of tightness" about his heart. There was no dyspnea nor edema, he had a good appetite and his bowels were regular. He had no nocturia.

Physical examination revealed a well-developed but very obese man 5 feet 6.5 inches in height, weighing 270 pounds, an increase of 80 per cent above his normal weight. His blood pressure was 190 systolic, 130 diastolic; pulse rate, 72. An examination of the chest gave normal findings, excepting that the heart showed a slight enlargement to the left, and a slightly accentuated second aortic sound but no murmurs. Blood examination: White blood cells, 10,000; red blood cells, 5,860,000; hemoglobin, 80 per cent. The blood Wassermann was negative. A phenolsulphonephthalein kidney function test showed an excretion of 15 per cent the first and 13 per cent the second hour. The basal metabolic rate was, + 28 per cent. Blood chemistry: Sugar, 95 mg.; urea, 33 mg.; uric acid, 3.1 mg.; creatinin, 1.1 mg.; nonprotein nitrogen, 39.9 mg.; plasma chlorids, 565 mg., per 100 cc. of blood.

The glucose tolerance curve, which is shown in Chart I (V) is normal, the curve returning to the normal level in two hours. There was no glycosuria, although the blood sugar rose to 193 mg. per 100 cc. of blood, thus indicating a high renal threshold. Because of this high renal threshold it would be very difficult to detect an early onset of diabetes by urinary examination alone. The data in this case therefore show that in spite of the large increase in weight the carbohydrate tolerance is normal.

Case VI (105,291).—This patient, a woman, aged forty-eight years, weighing 205 pounds, came to the Clinic because of pain in the right hypochondrium. Her father had died of cancer of the stomach but otherwise the family history contained no significant information. The patient had had none of the diseases of childhood; seven years before she had had an attack of gall-stone colic, which had not recurred.

Physical examination revealed a well-developed, obese woman, 5 feet 8 inches in height, whose normal weight would have been 158 pounds, so that she was 29 per cent overweight. She had a slight enlargement of the thyroid gland. Her blood pressure was 132 systolic, 80 diastolic. The physical examination gave normal findings excepting for tenderness over the gall-bladder region. A recent urine examination had shown a heavy glycosuria but no sugar was found in the examination of the urine made at the Clinic. Blood examination: White blood cells, 7800; red blood cells, 4,860,000; hemoglobin, 80 per cent. The blood Wassermann was negative. Blood chemistry: Sugar, 105 mg.; urea, 24 mg.; plasma chlorids, 585 mg., per 100 cc. of blood.

The glucose tolerance test, the curve of which is shown in Chart I (VI), indicates the presence of a mild type of diabetes with a renal threshold between 150 and 155 mg. of blood sugar per 100 cc. of

blood. In this case of obesity, therefore, we were dealing with an early stage of diabetes.

CASE VII (132,481).—This patient, a man aged thirty-six years, weighing 250 pounds, came to the Clinic because of headaches. His mother had died of cancer of the breast, but the family history contained no other significant information. There was no history of any of the diseases of childhood nor of any other illnesses, the patient stating that he had always been in good health. A year before sugar had been found in the urine during an examination for life insurance, but he had paid no attention to this finding, even though sugar had since been found in the urine on several occasions.

Physical examination revealed a well-developed, obese man. His height was 6 feet 2 inches, so that he was 35 per cent overweight. The only abnormal finding in the physical examination was an elevated blood pressure—155 systolic, 120 diastolic. The urine showed a trace of albumin and an occasional hyaline cast. Blood examination: White blood cells, 6400; red blood cells, 4,980,000; hemoglobin, 80 per cent. Blood chemistry: Sugar, 92 mg.; urea, 45 mg.; uric acid, 3 mg.; creatinin, 1.05 mg.; nonprotein nitrogen, 49.6 mg.; plasma chlorids, 595 mg., per 100 cc. of blood. The blood Wassermann was negative.

The findings in the glucose tolerance test are given in Chart I (VII), which shows that this obese man with hypertension had a normal tolerance for carbohydrates.

CASE VIII (164,227).—This patient, a woman, aged twenty-eight years, weighing 220 pounds, came to the Clinic because of shortness of breath. The family history was unimportant except that two sisters were stout. She gave no history of having had any of the diseases of childhood; but she had had frequent colds, and attacks of tonsillitis and of rheumatism. Curettage had been performed nine years before; and tonsillectomy and adenoidectomy two and a half years before. She had had a tubal pregnancy two years before; and had had five or six miscarriages. She stated that her feet swelled at times and that she had frequent suboccipital headaches. She drank a great deal of coffee. Eight years before she had weighed 105 pounds. She was 5 feet ½ inch in height, and was, therefore, 86 per cent overweight.

The blood pressure was 144 systolic, 90 diastolic; pulse, 112. The visual fields were normal. The basal metabolic rate was +12 per cent. The urine showed a faint trace of albumin and a few pus cells. The blood Wassermann was negative. Blood chemistry: Sugar, 95 mg.; urea, 33 mg.; uric acid, 4.2 mg.; creatinin, 1.3 mg.; nonprotein nitrogen, 41.3 mg.; plasma chlorids, 615 mg., per 100 cc. of blood.

The findings in the glucose tolerance test are given in Chart I (VIII), which shows a normal tolerance curve. The marked obesity in this case is of the polyglandular type, probaby principally due to ovarian dysfunction or insufficiency.

CASE IX (125,659).—This patient, a young woman, aged nineteen years, weighing 230 pounds, came to the Clinic because of nervousness and stomach trouble. The family history gave no significant information. Of the diseases of childhood she had had measles, mumps, and chickenpox; and later in life she had had attacks of tonsillitis and of rheumatism. Tonsil-

lectomy and adenoidectomy had been performed a year before. The patient stated that about every second week during the preceding year she had had a feeling of distress in the upper part of the abdomen which came on sometimes before and sometimes after eating. Eating made this distress worse and she belched gas but did not vomit. These attacks lasted from one to three days. She was very nervous and subject to frontal and occipital headaches. Her appetite varied but when it was good she ate heavily. Her gain in weight had been rapid between her tenth and eighteenth years and during the preceding five months she had gained

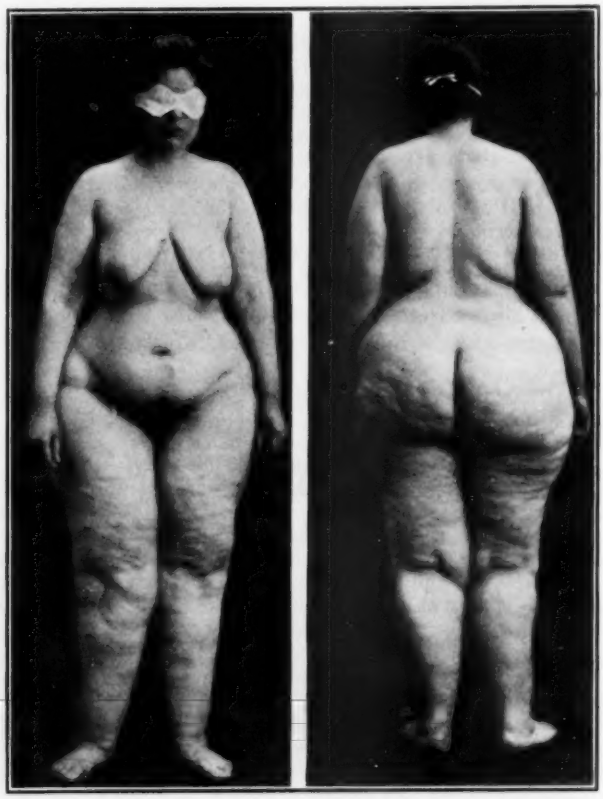

FIG. 1.—Photograph of Case IX described in text—showing the distribution of fat.

25 pounds. If she stood up for long periods she had edema of the ankles. Attacks of backache occurred after riding in an automobile. Her hands were cold but perspired most of the time. She was always tired and drowsy and exertion caused dyspnea. She had had no polyuria nor polydipsia. The menses occurred every three weeks and were very scanty in amount.

Physical examination revealed a (Fig. 1) marked adiposity of the lower part of the body. The patient was 5 feet 9 inches in height, so that she was 64 per cent overweight. She had a diffuse hyperplasia of the thyroid and a fine tremor of the hands. There was a slight murmur at the apex of the heart, which was not enlarged. The blood pressure was 128 systolic,

60 diastolic; skin, moist; hair, normally distributed over the body. A Roentgen ray examination of the skull showed no enlargement of the sella turcica. Blood examination: White blood cells, 8200; red blood cells, 4,100,000; hemoglobin, 80 per cent. Basal metabolic rate, −8 per cent. Blood chemistry: Sugar, 107 mg.; urea, 36 mg.; uric acid, 3.3 mg.; creatinin 1.3 mg.; nonprotein nitrogen, 41.4 mg.; plasma chlorids, 570 mg. per 100 cc. of blood. The blood Wassermann was negative.

The glucose tolerance test (Chart I (IX)) showed a lowered tolerance for carbohydrates, the blood-sugar curve reaching the normal level about three and a half hours after the ingestion of glucose. This curve indicates that the patient was in an early stage of diabetes. The diet, therefore, should be adjusted, especially by the reduction of carbohydrates, and the course of the patient should be followed. This case was one of adiposogenital dystrophia with a lowered carbohydrate tolerance.

Case X (107,355).—This patient, a woman aged thirty-six years, weighing 206 pounds, came to the Clinic because of the formation of gas in the stomach after meals. The family history gave no significant information. There was no history of any of the diseases of childhood nor of later illnesses. The patient stated that she had always been well until two months before when she began to notice a progressive, painless enlargement of the abdomen. She also had a slight shortness of breath after meals. The menses were regular.

Physical examination revealed a well-developed, obese woman 5 feet 5 inches in height who was 48 per cent overweight. The blood pressure was 128 systolic, 76 diastolic. The urine was normal except for a trace of albumin. The blood Wassermann was negative. Blood chemistry: Sugar, 111 mg.; urea, 25 mg.; plasma chlorids, 545 mg., per 100 cc. of blood.

The findings in the glucose-tolerance test are shown in Chart I (X). Although the blood sugar content at the beginning of the test was normal the curve did not reach the normal level again until almost three hours after the ingestion of glucose. The height of the curve was reached during the first hour and there was a slight lagging before it began to come down, thus showing a slight lagging in the carbohydrate tolerance. This patient therefore belonged in the group of cases which we call "prediabetic" in which the diet should be regulated and the progress watched.

Case XI (132,973).—This patient, a woman, aged twenty-seven years, weighing 205 pounds, came to the Clinic because she had not menstruated for fourteen months. The only fact of importance in the family history was that her father had died of duodenal ulcer. She had had none of the diseases of childhood, but had had tonsillitis and influenza. Her tonsils had been "clipped" nine years before. She stated that her menses had always been regular although scanty in amount. Five years before she had weighed 120 pounds. Her height at the time of this examination was 5 feet 4 inches so that she was 61 per cent overweight. She stated that she was a very small eater but nevertheless she kept on gaining weight. Recently she had been having severe headaches just above the eyes. There was no disturbance of vision. She had been drinking and voiding excessively and

perspiring freely. Exertion caused some dyspnea. She had poor endurance, slept poorly and was nervous.

Physical examination revealed an obese woman with an infantile uterus. There was no limitation of the visual fields. Roentgen ray examination showed the sella turcica to be normal. Urine examination revealed the presence of albumin and of a few casts. Blood examination: White blood cells, 13,900; red blood cells, 5,260,000; hemoglobin, 85 per cent. The blood Wassermann was negative. Blood chemistry: Sugar, 111 mg.; urea, 24 mg.; creatinin, 1.05 mg.; plasma chlorids, 555 mg., per 100 cc. of blood. The basal metabolic rate was +25 (in two estimations two months apart).

The findings in the glucose-tolerance test are shown in Chart I (XI). This is definitely a diabetic curve, showing a comparatively high renal threshold (at above 200 mg. per 100 cc.). From urine examination alone or from a fasting blood-sugar estimation, the diabetic condition could not have been identified so definitely. This case, therefore, was one of diabetic obesity, which, if allowed to go untreated, would eventually have developed into diabetic emaciation.

Case XII (104,338).—This patient, a man, aged thirty-nine years, came to the Clinic because of dizzy spells. His father had died from apoplexy at the age of forty-nine years, otherwise the family history presented nothing of importance. He had had none of the diseases of childhood, but had had typhoid fever at the age of sixteen years, and influenza three years before this examination. The patient stated that he had been having dizzy spells and headaches which had occurred only occasionally until during the preceding month, when the dizzy spells had occurred frequently and the headache had become continuous and so severe that he had had to stop working. For the most part the headache had been unilateral and in the right occipital region but it was occasionally frontal. The patient stated that he was not able to concentrate so well as formerly, and that he was excitable and nervous.

Physical examination revealed a well-developed, somewhat obese man who did not appear sick. A slight weakness on the left side of the face was noticed when he was talking. The reflexes were hyperactive; there was impairment of the seventh cranial nerve on the left side; the tongue deviated to the left. The eye grounds were normal. The urine showed a trace of albumin and heavy glycosuria. Blood Wassermann was anticomplementary. Blood chemistry: Sugar, 213 mg.; urea, 25.4 mg.; plasma chlorids, 614 mg., per 100 cc. of blood.

The glucose-tolerance test as in Chart I (XII), gave a definitely diabetic curve.

Summary.—1. Reports of 12 cases of obesity, 3 males and 9 females, are presented, in each of which the carbohydrate metabolism was studied by means of a glucose-tolerance test.

2. The overweight in these cases ranged from 29 to 115 per cent.

3. Glycosuria was present in 2 cases in both of which diabetes was present.

4. The fasting blood sugar was normal in 11 cases, among which 4 were cases of diabetes of varying degrees of severity.

5. Among these 12 cases of obesity, 2 were definitely cases of diabetes; 3 were case of mild diabetes or "prediabetics."

Conclusion.—Although this is a small series, the high incidence of a diabetic or prediabetic condition—42 per cent—in these cases of obesity indicates the importance of investigating the glucose tolerance in all cases of obesity to determine whether or not diabetes or a tendency to diabetes may be present.

It would appear, at least, that the pancreas is to be considered among the glands, the dysfunction of any of which may be responsible for obesity of the endogenous type.

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XANTHOMA DIABETICORUM: AN UNUSUAL PROCESS OF INVOLUTION.

By Eli Goldstein, M.D.,

and

John Harris, M.D.,

New York.

(From the Medical Service of Dr. Charles F. Tenney, the Fifth Avenue Hospital, New York City.)

The subject of xanthoma diabeticorum was thoroughly reviewed by Major who found 74 cases reported in the literature since this disease was first described by Addison and Gull in 1850.[1] In his own article, Major[2] described 4 cases, and subsequently 6 additional cases have been reported. It is our purpose in this communication to describe a case showing a peculiar process of involution not mentioned in the literature. This occurred in a patient suffering from diabetes mellitus, to whom insulin was administered in the late stages of the disease.

Case Report. S. C., male, Russian Hebrew, aged thirty-one years, tailor. Family history is negative. The patient does not remember any of the diseases of his childhood and gives no history of any

serious illnesses prior to the present affliction; denies syphilis and gonorrhea by name and symptoms. He is married and has three children living and well.

About three years ago he began to have symptoms of polyuria, polydipsia and polyphagia. Urine examination revealed the presence of 5 per cent glycosuria. Under a low carbohydrate régimen, these symptoms partially cleared up.

One year after the onset of the initial symptoms, he noticed small, discrete, yellowish nodules on the extensor surfaces of both legs. Six months later similar nodules appeared on both palms and elbows, and on the right thigh. The nodules gradually became confluent,

FIG. 1.—Palmar lesions.

and within several months after their onset those on the legs broke down, leaving large atrophic areas between which some of the original nodules could be readily distinguished. At no time was pruritus present. The same process occurred on the thigh, but did not involve the lesions on the upper extremities, which after attaining their maximum remained unchanged.

In the interim, he had disregarded his diet and consulted a chiropractor who gave him spinal adjustments for about one and a half years. On leaving the chiropractor's office after an adjustment May 27, 1925, the patient fell unconscious on the street, and was taken to a nearby hospital in a comatose condition, where it was found he had sustained a fracture of the base of the skull. He had marked ketonuria and a blood sugar of 430 mm. per 100 cc. of blood. Under insulin therapy he gradually recovered, and after a residence

of two weeks in the hospital was discharged with instructions to take 30 units of insulin three times a day, and to follow a low-carbohydrate diet.

At this stage the patient presented himself at our out-patient department, July 23, 1925, and stated he had no subjective symptoms. Physical examination revealed the following: well nourished, weight, 128 pounds; teeth in fair condition with some gingivitis; tonsils negative; heart and lungs normal; blood pressure, 120/80.

Skin. Both palms canary-yellow in color, presented semisolid, smooth, elevated, yellowish, peasized nodules distributed chiefly along the natural furrows (Fig. 1).* The elbows showed similar nodules of somewhat larger proportions, some of which had become confluent (Fig. 2). On the extensor surfaces of both legs and on

FIG. 2.—Elbow lesions.

the right thigh there were sharply defined areas of depressed, pigmented scars with festooned borders (Fig. 3). There was an interlacing network of these elevations upon the scars, the largest one being 5½ inches long and 2½ inches at its widest diameter on the left leg. In these scars the individual xanthoma nodules resembling those on the elbows, but undergoing this peculiar atrophic change, could be seen.

Histologic Examination (by Dr. David Satenstein; Biopsy Section from Leg). In the midcutis there is a more or less extensive infiltration, focal in places, but for the greater part diffuse. Smaller but similar areas are noted in the upper cutis, but not reaching to the epidermis. The infiltration is not in relation to the vessels. The epidermis is thinned but otherwise unaffected.

The infiltration is composed of more or less closely packed, long, polyhedral-shaped cells containing vesicular nuclei. In the proto-

* To Dr. Howard Fox we are indebted for the photographs and valuable suggestions in the preparation of this paper.

plasm of the cell are many very small and few larger vacuoles. The nuclei contain fine chromatin fibers and granules (xanthoma cells). In scattered places within the infiltration are rhomboidal-shaped spaces, marking the sites of former cholesterin crystals. Between and around the xanthoma cell areas are numerous fibroblasts, and occasional small bloodvessels with swollen endothelial cells. At the extreme margin of the section there is a large vessel with a proliferating endarteritis. The middle and external coats are not pathologic.

Diagnosis. Xanthoma with connective-tissue proliferation.

FIG. 3.—Lesions on the legs—note the individual xanthoma nodules.

Subsequent Course. The patient refused hospitalization, and was seen in the out-patient department for five and a half months. His diet averaged 1600 calories per day with a total carbohydrate value of 92 gm., and he administered to himself 75 units of insulin per day. It is doubtful whether he followed his diet, because during this entire period the urine was free from sugar only twice, and usually showed large amounts, at times with traces of acetone. However, in spite of the persistent glycosuria, definite improvement in the

skin lesions was observed after about six weeks' treatment. The lesions on the palms became flatter and paler, and some entirely disappeared. Those on the elbows and thigh showed similar changes but to a much lesser degree, whereas those on the legs remained unchanged.

Because of persistent glycosuria the patient was induced to enter the hospital December 5, 1925. He was placed on a diet amounting to 1200 calories and given 45 units of insulin a day. The glycosuria disappeared in two days, and the blood sugar, which had previously been estimated at 250 mg. per 100 cc., rapidly dropped to 160. He left the hospital December 21, on a diet with a caloric value of 1600, and with instructions to give himself 25 units of insulin three times a day.

During the next three months gradual improvement was apparent in his skin lesions. Those on the palms practically disappeared; those on the elbows became quite confluent and flatter and in some places completely disappeared. On the legs and thigh several of the remaining nodules could be seen undergoing the same atrophic change previously described, whereas the scars seemed to become thinner and paler, with a marked recession of the elevated festooned borders.

Within this period, he remained sugar free, although his blood sugar returned to a level of 250 mg. per 100 cc. Thereafter, however, and up to the present he has shown marked glycosuria. Blood plasma cholesterol taken just prior to his admission was 165 mg. per 100 cc., and frequent determinations never showed more than 306. Moreover, the blood plasma never had the milky gray appearance characteristic of lipemia. Repeated blood Wassermann tests were negative; the spinal fluid Wassermann test was negative (see chart).

Comment. 1. Apparently there is a definite relationship between the type of xanthoma nodule and the manner and rapidity of involution. As was emphasized by Balzer and Marie,[3] the miliary type disappears much sooner than the lenticular type, because as they say "we are dealing with elements in which an incipient organization of scar tissue retards resolution." In our case the palmar lesions corresponding to the "elements miliares" were first to improve, and two-thirds had disappeared before any improvement was noted in the "elements lenticulaires" present on the elbows, thigh and legs.

2. The question of the relationship of the glycosuria to the skin lesions has been raised by many authors. In most cases the disappearance of the glycosuria brought about either a marked improvement or a complete resolution of the lesions. The eruption, however, may disappear when the glycosuria and diabetic symptoms remain unchanged. On the other hand, diminution of sugar may find the xanthoma nodules unchanged or even worse.[4] In our case

the skin lesions began to resolve before any reduction in the glycosuria or blood sugar was accomplished. However, the rate of improvement was notably accelerated subsequently, and although slowly, the process is still going on in spite of the return to high blood-sugar levels and marked glycosuria. Whether or not insulin has any specific effect on the xanthoma lesions, has not been determined.

CHART SUMMARIZING LABORATORY FINDINGS AND CLINICAL COURSE WHILE UNDER OBSERVATION.

Date.	Glycosuria.	Bl. sug., mg.	Bl. chol., mg.	Diet, cal.	Insulin, units.	Remarks.
July 23, 1925	+++	...	...	1200	45	
Aug. 6, 1925	++++	200				
Aug. 18, 1925	++++	...	...	....	60	
Sept. 30, 1925	0					
Oct. 6, 1925	.....	...	...	1600	..	Xanthoma shows definite improvement.
Oct. 14, 1925	+++					
Nov. 11, 1925	+++	250	165	....	75	
Nov. 27, 1925	++++					
Dec. 5, 1925	++++	200	163	....	..	Entered hospital.
Dec. 7, 1925	0.6%	...	...	1209	45	Blood Wassermann negative.
Dec. 8, 1925	0	...	...	....	..	Spinal fluid Wassermann negative.
Dec. 17, 1925	0	160	306			
Dec. 19, 1925	0	125	...	1615	75	
Dec. 21, 1925	.....	...	...	....	..	Discharged from hospital.
Dec. 29, 1925	0	...	...	....	..	Marked progressive improvement in skin lesions.
Jan. 25, 1926	0	210	240	1615	75	
Mar. 15, 1926	++++	250	185			
April 24, 1926	++++	250	306	....	75	

3. In view of the fact that it is generally assumed that xanthoma diabeticorum occurs as a result of a disturbed fat metabolism, the cholesterol content of the blood plasma, which may be taken as an index of the lipemia, is significant. Of the 85 cases reported (including the authors') 12 give blood cholesterol findings. The average normal blood plasma cholesterol varies between 140 and 180 mg. per 100 cc. according to the method of Myers and Wardell, although somewhat higher figures are obtained by Bloor's technique. Every one of the 12 cases shows an increase in the cholesterol content which varies from 306 to 1800 (Engman and Weiss).[5] According to Major, and Lough and Killian[6] a fall in the blood cholesterol leads to an improvement in the xanthoma nodules. This is not borne out in the authors' case. The first cholesterol readings in our patient were within normal limits, and his highest was 306 at a time when

the xanthoma nodules had been undergoing rapid resolution, and in face of a blood sugar of 160. It would appear that although xanthoma diabeticorum is characterized by a hypercholesterolemia, the level of blood cholesterol need bear no definite relationship to the severity of the diabetes, the blood sugar and the xanthoma lesions themselves. Similarly, the presence of hypercholesterolemia, which is occasionally part of the diabetic picture, does not necessarily imply the presence of xanthoma.

4. The consensus of opinion in the literature reviewed is that when the xanthoma nodules undergo resolution, they disappear completely or at the most leave a pigmented area over the site of the lesion. Robinson[7] speaks of a small cicatrix at the site of the previous lesion. In his own words "after involution it mostly leaves no trace behind, but a few of the efflorescences are followed by hypertrophic cicatrices or hypertrophy of the skin."

Summary. We have here described a case of xanthoma diabeticorum in which three types of resolution went on simultaneously with little or no reference to the general condition: (*a*) The lesions on the palms disappeared completely; (*b*) those on the elbows coalesced and left large pigmented patches; (*c*) *those on the legs and thigh underwent degenerative changes resulting in extensive scar formation—a process hitherto undescribed.*

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DIABETIC ACIDOSIS WITH A NEGATIVE FERRIC-CHLORID REACTION IN THE URINE. REPORT OF FIVE CASES.

By Kenneth E. Appel, M.D.,

and

David A. Cooper, M.D.,

Philadelphia.

(From the Medical Division and the Pepper Laboratory of the Hospital of the University of Pennsylvania, Philadelphia, Penna.)

Clinicians commonly depend upon the examination of the urine by the ferric-chlorid reaction to indicate the presence or absence of diabetic acidosis. Evidence is accumulating that a negative reac-

tion does not necessarily preclude the presence of a severe and dangerous acidosis. There have recently been observed 5 cases of diabetes with a definite clinical picture of acidosis and a low plasma carbon-dioxid content, yet with a negative ferric-chlorid reaction in the urine. We shall give a brief résumé of the literature, present 5 cases, and offer a brief discussion of the possible explanations of this phenomenon.

In the early study of acidosis in diabetes, Stadelmann,[1] von Frerichs[2] and Lepine,[3] reported cases with apparently severe acidosis and absence of ketone bodies in the urine. In a brief communication Revillet[5] recorded a case of diabetic coma which had a negative ferric-chlorid reaction in the urine on the day of death. Rosenbloom[6] had 3 unusual cases of coma in which there was no trace of acetone, diacetic or β-oxybutyric acids in the urine, neither was there any evidence of kidney disease.

A fatal case of diabetic coma, whose carbon-dioxid combining power of the plasma was only 14.3 volumes per cent, while the urine contained only a trace of acetone and no diacetic acid, was reported by Feinblatt.[16] There was no acetone in this patient's blood, but it was present in the spinal fluid.

The lack of a definite relationship between urinary and blood ketones, and blood carbon dioxid, in cases of diabetic acidosis has been observed by a number of workers. Fitz[8] in several cases showed there was no definite quantitative relation between the acidosis as shown by the carbon-dioxid combining power of the plasma and the ketones of the plasma. The lack of a quantitative relationship between blood and urinary ketones was observed by Marriott.[10] Finally, Allen and Wishart[15] in a series of experimental studies on animals concluded that there existed no parallelism between ketonuria, ketonemia, and plasma bicarbonate content, and that death might ensue with either high or low plasma bicarbonate and with either high or low blood ketones.

The occurrence of cases of the type we are considering and records of observations such as are reported in the above paragraph, make our usual explanations of the physiology of diabetic coma and acidosis unsatisfactory in certain instances at least. Diabetic coma and acidosis is apparently not always directly due to an abnormal accumulation of ketone bodies in the blood. It was not unusual, therefore, that explanations were sought in other directions, as the following paragraphs show.

The factor of diminished blood base was early called attention to by Sellards.[4] He reported some cases in which the excretion of ammonia and acetone bodies was normal, but which showed a decrease in the titratable alkalinity of the blood together with an increased tolerance to bases. This was taken to indicate an impoverishment in base. Campbell[11] demonstrated that ketones could be made to disappear from the urine under insulin therapy without a corresponding increase in the plasma carbon dioxid.

Later, Campbell and Macleod,[12] in their review on insulin, attributed this phenomenon to a deficiency in base, or perhaps some unusual combination of bases that remain in the blood and tissues. They believed, therefore, that in such conditions the use of alkali was imperative.

An unknown acid of the ketone group was suggested, as an explanation of the phenomenon we are considering, by McCaskey.[7] He had had a fatal case of diabetic coma with neither diacetic nor β-oxybutyric acids in the urine. Bock, Field and Adair[13] reported several cases in which, after insulin therapy, the ferric-chlorid test in the urine became negative without a corresponding rise in the carbon-dioxid content of the plasma. They found 15 cases out of 68 patients, who died from diabetic coma showing slight or no ferric-chlorid reaction in the urine. They concluded that an unknown acid other than one of the ketone group was responsible for the acidosis and recommended the use of sodium bicarbonate. Cases in which other acids than those of the acetone group seemed to be a factor in the acidosis were reported by Starr and Fitz.[14] The concentration of unidentified organic acids in the urine they found to be in excess of normal, and the degree of acidosis in the blood greater than could be accounted for by the molecular concentration of the acetone bodies in the blood. They advised the administration of small doses of alkali in severe diabetic acidosis.

Impairment of kidney function, whether permanent or transient, remained to be considered. Paddock[17] reported a case with very high blood sugar, having no acetone nor diacetic acid in the urine, who died three hours after admission to hospital. The kidneys at autopsy showed a mild degree of subacute nephritis. The urine had a specific gravity of 1.020, a trace of albumin and a few hyaline casts. Argy's[18] case had the unusual blood sugar of 1714 mg. per 100 cc. with no acetone nor diacetic acid in the urine. There were many hyaline casts and a cloud of albumin. The non-protein nitrogen of the blood was 154 mg. Autopsy showed among other things, chronic parenchymatous nephritis, focal liver necrosis with fatty degeneration, and interstitial fibrosis of the pancreas. An interesting case was reported by John[19] in which the carbon dioxid in the plasma remained at a persistently low level in spite of large doses of insulin. A marked urinary retention developed, however. The blood urea was very high and the phenolsulphonephthalein output was greatly reduced. With improved kidney function the carbon-dioxid volume of the plasma increased. Edema of the tissues developed a few days after the inception of treatment. John suggested that perhaps the low carbon-dioxid values were due to kidney retention and edema of the tissues. Lemann[21] has recently reported a case which was in coma several times without showing acetone or diacetic acid in the urine. A nephritis, however, was found to coexist.

Peters[20] published an exhaustive study of the blood chemistry in diabetics. He stated that "severe ketonemia with minimal ketonuria as a terminal event in diabetes has been encountered not infrequently." Cases of severe diabetes, he found had a reduction in the total base and also in the plasma chlorids. When ketosis is of slow development it may reach a considerable degree of severity without affecting the plasma bicarbonate. In such cases the plasma chlorid is reduced and it is supposed that the base thus freed combines with the excess of organic acids for their neutralization. In more severe cases and those developing more rapidly, base is derived from both sodium chlorid and sodium bicarbonate, and hence both are lowered. As regards therapeusis, he believes that intravenous saline injections are logical. If the acidosis is due to an over-accumulation of ketone bodies, the proper adequate use of insulin and carbohydrate will eliminate them and the administrarion of sodium bicarbonate will tend to produce an alkalosis, especially as a considerable amount of base will be released by the combustion of the ketone bodies. He remarks that the acidosis in diabetic coma may be caused in part by acids not of the acetone group, but by acids formed as a result of associated pathologic processes. Case XXXVI, for example, in this series was in diabetic coma but had marked ketonuria and yet the serum contained only 13.5 millimols of organic acid, which is within the limits of normal.

Methods: The methods we have used in making the determinations reported here are given in Appendix I, at the end of the paper.

Case Abstracts. CASE I.—W. S., a white boy, aged seventeen years, was admitted (November 14, 1925) in a comatose condition and it was his third entry to the hospital in such a condition. He was a known diabetic for four years. His first admission, May 14, 1923, was ushered in by an attack of acute abdominal pain and vomiting. He had a high blood sugar, a low-plasma carbon dioxid and his urine contained sugar, acetone and diacetic acid. He improved on insulin and was discharged after four months with a blood sugar of 187 mg.

The second entry was on January 31, 1924. He showed a tendency to superficial abscess formation at the site of the insulin injections and had many scars from the abscesses. A culture from these lesions showed Streptococcus hemolyticus. He was discharged March 12, on the following diet: Protein, 50; fat, 105; carbohydrate, 50; insulin 30–10–15, units per twenty-four hours. The blood sugar was 142 mg. The urine showed a trace of albumin, sugar and acetone; but no diacetic acid. He was then under the supervision of the medical dispensary. Frequent colds, boils and some abscessed teeth, however, were his lot. The day before admission he developed labored breathing and became stuporous that night.

Past Medical History and Family History. Irrelevant.

Physical Examination. The temperature, pulse and respiration were 96°; 108; 34. Patient was semicomatose but could respond by answering "yes" and "no" to questions. He coöperated slightly on examination and could swallow. His lips were pink, his respirations deep and his breath had a fruity odor. The intraocular tension was decreased. There was considerable pyorrhea. Numerous scars of old infections presented on his thighs, and the left thigh was the seat of a large, red, fluctuating area.

TABLE I.

Case 1.—W. S.—Age, seventeen years; height, 170 cm.; weight, 114 pounds; basal requirements, 1650 calories.

Date.	Diet.				Insulin, units.			Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.				Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO_2 plasma.	Ketones.	
Nov. 20	4	0	789	3972	..	420*	..	7.30 A.M.	+++	+++	+++	319	11	..	White blood cells, 22/100; hemoglobin, 87 per cent; blood pressure, 116/65; semicomatose; temperature, 96°; pulse, 108; respiration, 34.
								3.50 P.M.	++	..	++	173	13		
								11.30 P.M.	+++	..	++				
Nov. 21	11	0	336	1388	..	117*	..	9.00 A.M.	+++	..	0	375	33	..	Blood culture, negative.
								1.15 P.M.	++	..	0				
								8.30 P.M.	+	..	0				
22	50	39	121	1035	20	20	20	8.40 A.M.	+++	..	0	385	33	..	Titrable acidity of 24-hr. urine, 325 cc., N/10 NaOH; blood urea nitrogen, 17
								9.00 P.M.	++	..	0	..	..	..	Phenolsulphonephthalein: 25 per cent in mg. 2 hrs.; 20 per cent in 5 hrs.; total, 45 per cent in 5 hrs.
23	58	41	116	1065	20	20	20	9.00 A.M.	++	..	0	385	46		Blood urea nitrogen, 23.
24	57	41	121	1081	20	20	20	...	136	++	+	327	51		
Dec. 24	57	104	53	1377	35	0	20	...	0	0	0				

* Total.

The heart was negative, but there were scattered rales throughout both chests. The abdomen was negative and knee jerks were not obtained. The urine on admission showed sugar ++++, and diacetic acid +++. The blood sugar was 319 mg. and the CO_2 content of the plasma was 11 volumes per cent. Table I is an abridged record of his stay in the hospital.

Clinical Notes. The carbohydrate given at first was in the form of orange juice reinforced with sucrose. This was given by mouth. Enteroclysis of 3 per cent sodium bicarbonate and 5 per cent glucose was also given. There were no intravenous injections and no alkali was given by mouth. Large doses of insulin were given hypodermically, 420 units in the first twenty-four hours and 117 the next. Frequent urine analyses were made to prevent overdosing and hypoglycemia.

The interesting feature of this case is the fact that for thirty-six hours at least, the urine was free from diacetic acid according to the ferric chlorid test, and yet, the carbon-dioxid content of the plasma was only 33 volumes per cent. The discrepancy between the absent ferric-chlorid reaction in the urine and the low carbon-dioxid content of the plasma need explanation. There was some evidence of impaired renal function, for the urine contained a cloud of albumin, few epithelial, and many light granular casts.

On the third day the phenolsulphonephthalein test showed delayed elimination. The fourth day the blood urea nitrogen was slightly increased. We had no further test of the blood urea or phenolsulphonephthalein elimination, but the urine itself cleared up, except for a very faint trace of albumin. The impression was held, therefore, that the kidney was suffering only a temporary or functional disability. Even at that time, however, its output of total acids was in the normal range.

Case II.—M. Q., a white female, was admitted (January 8, 1926) in coma; but her physical condition was such that she was sent to the surgical wards with the possibility of an acute abdomen. Her abdomen was apparently rigid and her leukocytes 30,000. This rigidity, however, was later decided to be only inspiratory and not due to visceral disease.

History of Present Illness. Patient was a known diabetic with characteristic symptoms of three years' duration. She was well controlled by diet and insulin until December, 1924, when, after discontinuing insulin for one week, she went into coma. This cleared up in four days with insulin and she did well until December, 1925, when she began to disregard her diet. Four days before admission she developed epigastric pain and sweating. She grew progressively weaker, felt drowsy and finally went into the condition described on admission. There was no history of an acute infection.

Previous Medical History. Quinsy at twelve years of age.

Family History and Social History. Irrelevant.

Physical Examination. Temperature, pulse and respiration 96°; 104; 17. The breath had a strong odor of acetone. The respirations were deep and grunting. The skin was dry and loose. The patient could scarcely be aroused enough to say "yes" or "no."

The blood pressure was 100 to 80 and the radial pulses were of poor volume and tension. There was a short, blowing, systolic murmur over the base of the heart—not transmitted. The knee jerks could not be elicited. The examination was otherwise negative. The urine showed sugar, +++; acetone, +++; diacetic acid, +++. The blood sugar was 482 mg. per 100 cc. and the plasma CO_2 had the low figure of 6.8 volumes per cent. Table II gives a summary of the essential features of the case.

Clinical Notes. The simulation of a surgical condition on entry was an interesting feature of this case. The apparent rigidity and leukocytosis were misleading factors. It was later decided that the rigidity was only

TABLE II.

TABLE II.

Patient, M.Q.—Age, forty-seven years; height, 5 feet; weight, 102 pounds; basal requirements, 1200 calories.

Date.	Diet.				Insulin, units.	Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO_2 plasma.	Ketones.	
Jan. 9	..	..	..	..	.. .. ..	5.30 P.M.	+++	+++	+++	482	6.8	..	Comatose; blood pressure ,100/80; temperature, 96°; pulse, 120; respiration, 24.
	0	0	265	1060	.. 180* ..	...	Tr.	+	0	77	27	..	Hemoglobin, 120 per cent; red blood cells 5,900,000; white blood cells, 24,000; blood urea nitrogen, 43 mg.; urine, albumin, cloudy, no casts.
						11.00 A.M.	Tr.	Tr.?	0	..	..	40.4	Phenolsulphonephthalein: 1st hr., trace, 2d hr., 28 per cent; 4th hr., 20 per cent; total in 4 hrs., 40 per cent. See special chart. Table IIa.
						10.00 P.M.	+	..	0				
10	25	30	120	850	.. 20 ..	...	+	Tr.?	0	..	..	..	Urine, trace of albumin; occluded hyaline casts.
						10.30 A.M.	+++	Tr.?	0	470	20	..	White blood cells, 17,300; hemoglobin, 105 per cent; 12-hr. urine, 760 cc.; total acidity, 180 cc., N/10 NaOH.
						6.00 P.M.	+++	..	+	..	..	..	Blood pressure, 140/90; stuporous.
						10.00 P.M.	+++	..	Tr.				
11	46	34	289	1566	.. 215* ..	24-hr. sp.	4.9	+	0	44	48	..	Urine, albumin, cloudy, hyaline casts.
						4.00 P.M.	0	0	0				
12	39	27	255	1419	.. 65* ..	...	36.7	0	0	89	48		
13	50	46	85	954	.. 30* ..	...	7.5	0	0	201	61		
19	51	100	76	1408	20 0 5	...	+	0	0	261	..	..	Blood urea nitrogen, 17 mg.; phenolsulphonephthalein: 1st hr., 55 per cent; 2d hr., 5 per cent; total in 2 hrs., 60 per cent.

* Total.

inspiratory and the urine analysis pointed the way to the diabetic condition. Other cases of ours have shown a leukocytosis, the degree of which probably cannot be accounted for by dehydration if we use the hemoglobin percentage as an indication of the degree of dehydration. Neither can the leukocytosis be accounted for here on an infectious basis for we were unable to find a focus of infection; and Roentgen rays of teeth, sinuses and gall bladder, were negative. There is, perhaps, some factor associated with the metabolism of diabetic coma which chemically stimulates leukocytes. Peters[20] in his article reported that several of his patients narrowly escaped the surgeon's knife because of a simulated acute abdominal condition.

During the first twelve hours in the hospital it became difficult for the patient to swallow. Through a nasal tube, feedings of orange juice were then given. But rather intractable vomiting developed and we were considering intravenous injections, when we tried milk sweetened with sugar and found that this was well tolerated.

It seemed almost as if the patient had a specific sensitivity to orange juice for immediately after vomiting orange juice, milk was kept down. Grape juice, prunes, bananas, toast and sweetened milk were tolerated when orange juice and oat-meal actually induced vomiting. The patient ultimately came out of her coma completely, although we did not expect it, and she left the hospital before her diet had been adequately adjusted.

Twelve hours after admission there was an absent ferric-chlorid reaction in the urine together with a CO_2 content of the plasma of from 20 to 27 volumes per cent. These combined findings persisted for over twenty-four hours. If we had judged alone from the ferric-chlorid test and the improved mental state of the patient, we certainly should not have imagined that the carbon-dioxid content of the plasma was so low as 20 volumes per cent. It is obvious that these rather simple laboratory and clinical tests are not always, at least, indicative of the degree of "acidosis" that actually exists.

Impaired renal function occurred in this case as was indicated by: (1) A cloud of albumin and casts in the urine; (2) a blood-urea nitrogen of 43 mg.; (3) a phenolsulphonephthalein test which showed only a trace the first hour, 28 per cent the second, and 20 the fourth, making a total of 48 per cent in four hours.

As in the previous case, however, the renal function was only temporarily impaired, for later the blood urea nitrogen fell to 17 mg.; the phthalein test was 60 per cent in two hours; and the urine showed only a very faint trace of albumin. The decreased kidney function could not have been due to circulatory collapse for the blood pressure the day after admission was 105 to 80, approximately the same as on entry. One might suppose that a sort of functional or transient nephritis existed on a dehydration basis, for the hemoglobin of 120 per cent certainly was evidence of this.

Table II*a* shows determinations* of the plasma electrolytes for the patient, and also figures for the normal person. The blood ketones were increased

TABLE II*a*

Plasma Electrolytes.

Patient.			Normal.		
Cations (m. equiv.).	Anions (m. equiv.).		Cations (m. equiv.).	Anions (m. equiv.).	
Total, 126	HCO_3 . .	11.5	Total, 150	HCO_3 . . .	26
	Cl . . .	97.3		Cl	103
	PO_4 . . .	0.5		PO_4 . . .	3
	Ketones . .	4.9		SO_4 . . .	1
	Proteins† .	12.0		Prot. . . .	17

* Our thanks are due Dr. Austin, of the Department of Research Medicine, for these and other analyses, and his kind coöperation.

† Difference.

but not enough to account for the decrease in the CO_2. The latter is accounted for by another determination, viz., the total base of the plasma. In our patient, the measurement of total base equalled 126 milliequivalents. Lowered total base then in part accounts for the total CO_2 content of the plasma. Peters[20] made numerous determinations in diabetics and found the same condition of plasma electrolytes. Our case is merely a single confirmation of his observations. It shows the mistaken reasoning that can follow the finding of an absent ferric-chlorid reaction in the urine, and that the plasma CO_2 content may leave one with wrong conclusions according to one's usual reasoning about low CO_2 and acidosis.

Case III.—L. C., a white female, aged forty-two years, was admitted January 7, 1926.

Chief Complaint. Weakness. Sense of oppression in chest. Indigestion. Tapeworms.

History of Present Illness. The patient had lost considerable weight in the past several years. Six months before entry she had noticed paraesthesia of the fingers and toes. She passed large quantities of urine and had nocturia two to three times. One week before admission the patient had a sudden attack of indigestion which was characterized by vomiting and gaseous eructations. Associated with this there was a sense of oppression in her chest. She was confined to bed and grew progressively weaker until the time of admission.

Past Medical History. Tapeworm infestation seven years ago and has continued to pass segments occasionally since. Breast abscess seven years ago.

Family History. Irrelevant.

Physical Examination. Temperature, pulse, respiration, 97°; 104; 20. Blood pressure 138/82. Patient was a poorly developed, emaciated and dehydrated woman. She was sluggish mentally. Her tongue and pharynx were exceedingly dry and red. Over the apex of the heart there was a faint systolic bruit. The knee and ankle jerks were not elicited. Examination was otherwise negative. The urine on admission showed negative albumin; sugar, ++; acetone, +++; and diacetic acid, ++. The leukocytes were 16,000 and the hemoglobin, 100 per cent. The accompanying table gives the important points in this case.

Clinical Notes. Attention is called in this case to the following: 1. The occurrence of a low plasma CO_2 content (22 to 37 volumes per cent) for a period of over twenty-four hours, with a negative ferric-chlorid reaction in the urine, on repeated examinations.

2. With a negative ferric-chlorid reaction in the urine, the blood ketones were 50.7 mg. per 100 cc., a figure well above normal. This suggested the possibility of a high renal threshold for ketones.

3. There was also a retention of urea nitrogen (57 mg. per 100 cc.) and a delayed phthalein elimination (first hour, 7 per cent; second hour, 50 per cent) together with albumin and casts in the urine. These evidences of nephritis cleared up later with the disappearance of the dehydration, as was shown by a blood urea nitrogen of 12 mg. per 100 cc., a phthalein test of 50 per cent the first hour and 5 per cent the second, and a urine negative for albumin and casts.

4. The importance of the hemoglobin percentage as an indication of dehydration (100 per cent on admission and 70 per cent on the fifth day).

5. It is of interest to note that in spite of a plasma carbon dioxid of 22 volumes per cent there was no noticeable hyperpnea.

6. A possible factor which perhaps precipitated the acidosis in this case was an old intestinal infestation with Tenea Saginata, for segments were found in the feces during the patient's residence in the hospital.

TABLE III.

Patient, L. C.—Age, forty-two years; height, 5 feet, 2 inches; weight, 96½ pounds; Basal requirements, 1220 calories.

Date.	Diet.				Insulin, units.			Urine.				Blood			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.				Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO_2 plasma.	Ketones.	
Jan. 8	..	..	190	760	..	90*	..	...	+++	+++	+++	316	22	..	Hemoglobin, 100 per cent; white blood cells, 16,000.
								1.00 P.M.	+++	..	0				
9	58	34	120	818	..	60*	..	...	55	+	0	211	37	51+	Blood urea nitrogen, 57 mg.; phenolsulphonephthalein: 1st hr., 7 per cent; 2d hr., 50 per cent; total 2 hrs., 57 per cent.
13	56	104	52	1368	20	10	15	...	6.4	+	0	242	64	..	Hemoglobin, 70 per cent; white blood cells, 8400.
16	..	..	..	..	..	..	..	...	..	..	..	..	..	..	Blood urea nitrogen, 12 mg.; phenolsulphonephthalein: 1st hr., 48 per cent; 2d hr., 5 per cent; total 2 hrs., 53 per cent.
Feb. 28	50	140	70	1740	15	0	10	...	0	0	0				

* Total.

CASE IV.—E. G., a white female, aged fifty-seven years, was admitted January 20, 1926.

Chief Complaint. Dimness of vision. Generalized weakness.

History of Present Illness. The onset of the patient's diabetic symptoms occurred eleven years before entrance to the hospital, with itching of the skin, excessive thirst, polyuria, nocturia, and a craving for sweets. Five years before admission the patient had an ulcer on her foot and came to this hospital for treatment. At that time her blood sugar was found to be 300 mg. per 100 cc.; her blood urea nitrogen 33 mg., and her blood pressure was 128/70. Her urine showed a trace of sugar, a cloud of albumin, and a few hyaline and light granular casts. The phenolsulphonephthalein test was 35 per cent on admission and 65 per cent on discharge.

Physical examination was essentially negative. After six weeks she was discharged sugar free, with a blood sugar of 172 mg. and a blood urea nitrogen of 26 mg. per 100 cc. The diagnosis on discharge was chronic nephritis and diabetes mellitus. Since leaving the hospital she had been under her physician's care and remained sugar free. However, during the past four months she noticed increasing dimness of vision and an occasional headache. Her bowels were constipated.

Past Medical History. Irrelevant.

Physical Examination. Temperature, pulse, respiration, 98°; 96; 26.

The patient was a well-developed, somewhat fat, woman, aged fifty-seven years. Her vision was markedly impaired. Her pupils were equal, slightly irregular, and reacted poorly to light.

The fundi showed numerous hemorrhages, exudates and areas of atrophy. The brachial vessels were tortuous and thickened. Her blood pressure was 215 to 115. The heart was slightly enlarged, with sharp sounds of embryonic quality. There was a precordial, systolic murmur. The lungs were negative and the abdomen pendulant. The extremities were negative and the arteries were felt pulsating at both ankles. Urine showed: A trace of sugar with acetone and diacetic acid negative; a cloud of albumin; no casts; no red cells and two pus cells per high-power field. The hemoglobin was 74 per cent and the leukocytes 7600. Table IV is an abridged record of this case.

Clinical Notes. The combination of diabetes and nephritis in this patient makes some of our determinations more interesting. On entry there was no clinical evidence of acidosis. We were surprised on the following morning to find the CO_2 content of the plasma 38 volumes per cent. With a phenolsulphonephthalein excretion of only a trace in two hours and a blood-urea nitrogen of 56 mg., we concluded that the condition was chiefly nephritic. We placed the patient on a low-protein, low-salt, diet with rather high carbohydrates and fat. She had shown only a trace of sugar, no diacetic acid nor acetone, and her blood sugar was only 164 mg. per 100 cc. On this régime we gave her 15 units of insulin in the morning.

Six days after admission, with the treatment as above outlined, we found the blood and urine analyses approximately the same as on entry, but the patient felt better subjectively. Her blood pressure was lower, her headaches were not so severe and her vision was slightly but definitely better. The following day, however, the CO_2 content was 29 and 27 volumes per cent, respectively, on two determinations three hours apart. The urine contained sugar, +; no diacetic acid; no acetone. There was, however, a heavy cloud of albumin but no casts. It was felt on this day that the patient's general condition was improving, until we received the report of the low CO_2 content of the plasma.

The following day the ketones of the blood were determined and to our astonishment they were 153 mg. per 100 cc., with no acetone nor diacetic

TABLE IV.

Patient, E. G.—Age, fifty-seven years; height, 5 feet, 5 inches; weight, 145 pounds; basal requirements, 1440 cal

Date.	Diet.				Insulin, units.			Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.				Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO_2 plasma.	Ketones.	
Jan. 23	51	153	79	1897	..	..	..	...	Tr.	0	0	164	38	..	Hemoglobin, 74 per cent; phenolsulphonephthalein, trace in 2 hrs.; blood urea nitrogen, 56 mg.
25	36	119	130	1734	15	0	0	...	+	0	0	164	..	..	Blood urea nitrogen, 42 mg.; blood uric acid, 4.8 mg.
29	36	122	132	1770	15	0	0	...	+	0	0	180	42	..	Blood urea nitrogen, 50 mg.; urine: sp. gr., 1010; albumin, cloud; casts, few, waxy, epithelial and granular.
30	38	142	106	1842	15	0	0	2.00 P.M.	+	0	0	..	29	..	See Chart.† IVa.
								5.45 P.M.	0	0	0	..	27		
Feb. 2	34	124	122	1740	15	0	0	...	0	0	0	173	24	153	Blood urea nitrogen, 49 mg.; blood pressure, 180/94.
9	28	121	58	1426	15	0	0	...	0	0	0	252	..	..	Blood urea nitrogen, 100 mg.
12	..	..	70	280	0	0	40	...	Incontinent			182	27	..	Blood urea nitrogen, 152 mg.; comatose.
13	9	1	180	804	..	70*	..	...	0	0	0	..	..	16	Urine: albumin, cloud no casts. Death, 8.35 P.M.; autopsy not permitted.

* Total.

acid in the urine. The CO_2 content was 24 volumes per cent and the blood urea nitrogen 49 mg. Obviously we had unwittingly allowed the ketones to develop in the blood, but neither the clinical condition of the patient (no dyspnea nor increased drowsiness) nor the urine analysis gave us a clue to the real state of the metabolism. The threshold for ketone body elimination was obviously raised by the actual nephritis. The day following these determinations, the patient developed hyperpnea and the blood urea rose to 100 mg. per 100 cc. of blood. Increased doses of insulin were given to reduce the ketonemia but the patient steadily failed, went into coma and died three days later. Her blood ketones had been removed, however, by the increased insulin, for on the day of death the blood ketones were only 16 mg. per 100 cc. The blood urea, however, mounted to 152 mg., the day before exitus.

Table IV*a* records some observations made on January 30, 1926, when there was no acetone nor diacetic acid in the urine according to the ferric-

TABLE IV*a*.

Plasma electrolytes.

Patient.			Normal.		
Conductivity of plasma.	Plasma protein by refractometer.	Depression of freezing point.	Conductivity of plasma.	Plasma protein by refractometer.	Depression of freezing point.
0.822	9.7%	59	0.785–0.810	7%	54–57

chlorid test, with a CO_2 content of the plasma of 29 to 27 volumes per cent. Normal figures are given for comparison. The conductivity of the patient's plasma was increased and this is taken as an indication of increased base in the plasma. The determination of the CO_2 content of the plasma leaves us ignorant as to the amount of total base in the plasma, whether it has decreased, in carrying out ketones and end products in the urine, or whether merely the base is combined and not available for other acids. The determination of the plasma conductivity in this case shows us that (although the CO_2 content is low) the total base is somewhat above normal and that it is, therefore, probably combined with acid products of metabolism, although the urine has not given us indication of this.

Case V.—M. R., a white female, aged sixty-four years, was admitted February 2, 1926.

Chief Complaint. Coma.

History of Present Illness. The patient was a retired physician who came into the Hospital in a semicomatose condition. The history was unsatisfactorily obtained. She had apparently had glycosuria, however, for almost a year, but had apparently controlled her diabetes by diet alone, for she never had taken insulin. The day of entry she became drowsy and developed deep, sighing respirations. A local physician visited her and sent her to the hospital.

Previous Medical and Family History. One breast was removed for cancer several years before entry. A brother had severe diabetes.

Physical Examination. Temperature, pulse, respiration, 96°; 116; 40.

The patient was in a semicomatose condition but responded intelligently, although slowly, when pressed for answers. She coöperated on examination, and with the nursing, and was able to swallow. She was hyperpneic, had pink lips, and acetone on her breath. She was thin and somewhat dehydrated. Her blood pressure was 65/40. The heart was negative and there was nothing unusual in the chest. The abdomen was also negative

TABLE V.

Patient, R.—Age, sixty-four years.

Date.	Diet.				Insulin, units.	Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO_2 plasma.	Ketones.	
Feb. 2	..	..	..	..	.. .. ..	...	+++	++	0	450	14.7	194	Comatose; blood pressure, 65/40; blood urea nitrogen, 47 mg.; plasma proteins, 77 per cent; hemoglobin, 80 per cent; white blood cells, 24,900. See Table Va.
						11.00 P.M.	+++	+	0				
			520	..	.. 250*								
3	..	..	..	..	.. .. ..	9.00 A.M.	++	0	0	468	39	..	Urine: albumin, very faint trace; casts, many hyaline and few granular.
						3.00 P.M.	..	..	..	353			
						7.30 P.M.	Tr.	..	0				
						8.00 P.M.	..	..	..	150			
3	..	..	90	360	.. 100*								
						9.20 P.M.	..	..	..	..	..	..	Death.

* Total.

and the knee jerks were normal. There was no evidence of infection. Urine examination showed: Specific gravity 1.020; a cloud of albumin; positive sugar; acetone, ++; diacetic acid negative; a few waxy and hyaline casts; no red blood cells and three white blood cells per high-power field. The blood sugar was 450 mg. per 100 cc. and the CO_2 content of the plasma was 14.7 volumes per cent. The blood urea nitrogen was 47 mg. and the plasma proteins were 7+ per cent determined by the refractometric method. Her hemoglobin percentage was 80 and the leukocytes were 24,900. About twenty-six hours after entry she became unconscious and died three hours later. Table V is an abstract of her record.

Clinical Notes. The patient's record shows that she never had a positive ferric-chlorid reaction in the urine, yet she unquestionably died of diabetic coma. She was considered a mild diabetic and the day she became drowsy it was not believed that a condition was developing which called for rapid action. An analysis of her urine by the ferric-chlorid method would not warn us that acid poisoning was threatening. The low CO_2 content of the plasma showed us that an advanced acidosis existed but this test of course, is not available in the home.

We note in her chart a high value of blood ketones (194 mg. per 100 cc.) with an absent ferric-chlorid reaction in the urine. Some of the urine analyses were made on catheterized urine. Two hours before death a catheterized specimen showed only a trace of sugar and no diacetic acid.

Table V*a* shows some further determinations made on the blood taken on entry which showed a low CO_2 content, and a high sugar and ketone content. The conductivity which is lower than normal, indicates a lowered plasma base. The protein content indicates dehydration.

TABLE V*a*.

Plasma electrolytes.

Patient.		Normal.	
Conductivity of of plasma.	Plasma protein by refractometer.	Conductivity of plasma.	Plasma protein by refractometer.
0.704	8.4%	0.810–0.785	7%

An autopsy was performed which showed a rather friable liver in the gross with nothing characteristic microscopically, a pancreas exceedingly infiltrated with fat, a heart with brown atrophy and kidneys with no gross or microscopic evidence of nephritis. The threshold for ketones here, therefore, was not raised by a *true nephritis* but probably was due to a *transient or functional nephritis* again on a dehydration basis.

Discussion. In the present report we have presented the records of 5 patients suffering with diabetes mellitus, who at some time in the course of this disease presented the unusual combination of a low CO_2 content of the plasma with a negative ferric-chlorid reaction in the urine. The possible explanations of this condition are:

1. A transient, functional nephritis, or better, temporarily impaired renal function on a basis of dehydration causing a high threshold for both blood ketones, nitrogenous and other acid products of metabolism.

2. Actual nephritis with diabetes, causing a retention of the same products as in 1.

3. Lowered base in the plasma.

4. Unknown acid in the blood.

5. A combination of the above explanations.

6. An unusually rapid decomposition of diacetic acid into acetone in the urine.

We believe the following explanations account for our various cases:

Case I. Possibly mechanisms 1, 3, 4. We had definite evidence of impaired renal function in the urine (which later cleared up) and in the phenolsulphonephthalein test.

Case II. Mechanisms 1, 3. There is no doubt that temporary renal impairment existed here for we had a pathologic urine (a cloud of albumin and casts), a pathologic blood (urea nitrogen 43 mg.) and a pathologic phenolsulphonephthalein test (trace in the first hour, 28 per cent in the second). After clinical improvement all of these values returned to normal. The renal impairment was not caused by circulatory failure, neither was it caused by infection, because both of these factors were wanting. The most probable explanation seems to us to have been dehydration and the hemoglobin percentage of 120 was ample evidence of this. We might picture therefore, a sort of functional nephritis existing on the basis of dehydration and that the threshold for ketone body and other acid products of excretion was elevated. Such a dehydration acidosis is known to exist in diseases of infancy and childhood.[9]

The question comes up then as to whether the transient nephritis could have accounted for the acidosis. Actual determinations, however, showed an increase in the acid products of the blood, but not sufficient to account for the low CO_2 content of the plasma. The figures in Table II show an increase in blood ketones above normal. Normal blood contains less than 4 mg. of hydroxybutyric acid and 1.5 mg. of acetone and diacetic acid per 100 cc.[22,29] In the patient's blood we found 40.4 mg. of ketone bodies—a figure definitely above normal, but the increase in ketones is not great enough to account for the decrease in CO_2. The latter is accounted for by the lowered total base in the plasma. In our patient the measurement of total base equalled 126 milliequivalents, whereas normal blood contains 150 milliequivalents.

We have in this case, substantial evidence of a temporary impairment of renal function which no doubt raised the threshold for blood ketones which were increased, and which, therefore, in part accounts, no doubt, for the absent ferric-chlorid reaction in the urine. The mechanisms of the lowering of the CO_2 in the plasma we have accounted for in the preceding paragraph and it is a mechanism of physiology which one usually does not think of when he obtains a low plasma CO_2 in diabetic acidosis. With such findings, we

believe, it is rational to consider intravenous sodium chlorid or possibly sodium-bicarbonate injections.

Case III. Mechanism 1, possibly 3.

Case IV. Mechanisms 1, 2. This case presented the combination of severe, fatal chronic nephritis with a moderate diabetes. It, therefore, furnished almost a laboratory experiment of the effect of renal-function impairment on the threshold for ketone-body excretion. With the blood ketones at a level of 153 mg. per 100 cc., no acetone or diacetic acid, was found in the urine by the usual tests! There was, too, some dehydration as the refractometric examination of the blood showed.

If we convert the ketone (153 mg. per 100 cc.) and CO_2 (24 volumes per cent) values into milliequivalents, we have 26.4 and 10.7 milliequivalents, respectively. The lowering in the CO_2 did not release, therefore, sufficient base to combine with this amount of ketone bodies. The assumption may be made therefore, that the chlorids were reduced and yielded increased base, and that the shifting of the pH toward the acid side released more base from the plasma proteins. As a matter of fact the electrical conductivity measurement showed an increase over normal, which is an indication of increased base in the plasma. The determination, alone, of the CO_2 content of the plasma leaves us ignorant as to whether the total base of the plasma has decreased (in carrying out ketones and end products in the urine) as for example in Case II; or whether merely the base is combined and not available for other acids.

Case V. Mechanisms 1, 3.

Autopsy in this case proved that there was no actual nephritis; yet this patient went into diabetic coma and died without showing a positive ferric-chlorid reaction in the urine. With blood ketones at 194 mg. per 100 cc. the ferric-chlorid reaction in the urine was negative and this on catheterized urine. We believe, therefore, that this case indicates a purely functional (as contrasted to the previous case) renal impairment which raised the threshold of ketone body elimination. Dehydration, as shown by the refractometric examination of the blood, and low blood pressure, no doubt, contributed to this functional renal disability. The conductivity measurements (Table V*a*) indicate that the plasma base was somewhat below normal.

Joslin[23] says that "the simplest method for the detection of acidosis by urinary examination is Gerhardt's ferric-chlorid reaction for diacetic acid."

This test is used, no doubt, by the majority of physicians and patients for the detection of acid poisoning. Certainly diacetic acid usually increases in the urine when coma approaches and Hurtley[24] states that "the ratio of aceto-acetic to hydroxybutyric acid in the urine increases with the severity of the intoxication." Case V in our series did not show a positive ferric-chlorid reaction

on entry and yet she died in less than thirty-six hours without ever showing this reaction. The point should be made, therefore, that an absent ferric-chlorid reaction does not preclude the diagnosis of threatened diabetic coma and if a diabetic is feeling ill it is unwise for him not to call a physician because the urine does not give a positive ferric-chlorid reaction.

The ferric-chlorid reaction in the second place is frequently used as an indication of the progress made in the treatment of a case of diabetic coma. One usually concludes that when the ferric-chlorid reaction becomes negative in the urine, that the case is under good control. As we have seen, our cases have shown at one time or other in the course of the disease a degree of acidosis as indicated by the CO_2 content of the plasma which we should not have supposed to exist from the ferric-chlorid test in the urine. One cannot relax one's efforts at treatment, therefore, when the ferric-chlorid reaction first becomes negative in the urine.

We have not discussed the possibility of an unusually rapid decomposition of diacetic acid into acetone in the urine. We have merely made certain observations. Many of our urine analyses were made on catheterized specimens and were repeatedly checked, so that if a transformation took place, it must have occurred in the bladder. Wells[25] quotes Folin as saying that fresh diabetic urine does not contain acetone and that when a test for the latter is obtained it is due to the decomposition of diacetic acid. The only way we could have obtained fresher urine would have been by ureteral catheterization.

Clinically, however, our fresh diabetic urine showed positive reactions for acetone. We used, however, the sodium nitroprusside reaction and Folin[26] says that the acetone tests used by clinicians are really tests for diacetic acid. The nitroprusside reaction Mathews[27] and Folin (*ibid.*) point out, is much more sensitive for diacetic acid than the ferric-chlorid reaction. The former being sensitive to one part in 30,000; while the latter is sensitive only to one part in 7000. Clinicians have usually spoken of the one as being a test for acetone and the other for diacetic acid. It appears, therefore, that they have not been correct in this and that the point of the tests has been in the significance of the *amount* of diacetic acid in the urine as an indication of acid intoxication.

Conclusions. An absent ferric-chlorid reaction in the urine:

1. Does not preclude the diagnosis of threatened diabetic coma.
2. In a case of diabetic coma under treatment does not always mean that the case is well under control.
3. Does not mean necessarily that the plasma CO_2 content is out of the acidotic range.
4. Cannot be taken to indicate that the blood ketones are not greatly increased.

5. As an explanation of an absent ferric-chlorid reaction in the urine in threatened diabetic coma, in advanced diabetic coma under treatment, in diabetic coma with a low CO_2, in diabetic coma with considerably increased blood ketones, we suggest that the absence is probably due to temporary renal impairment usually on a basis of dehydration.

APPENDIX I. Methods used in making determinations.

Urinary sugar was tested both by Benedict's and Fehling's methods.[26]

Urinary acetone and diacetic acid were tested by the usual sodium nitroprusside + ammonia, and ferric-chlorid, reactions respectively.[26]

Blood sugar and urea-nitrogen determinations were made by Folin's method.[26]

Blood plasma carbon-dioxid content was determined by the van Slyke method.[28]

Blood-acetone determinations were made by van Slyke's method.[29]

Total base was determined by the method of Stadie and Ross.[30]

Plasma chlorids were determined by the method of van Slyke.[31]

Freezing-point determinations were made by the cryoscopic method of Burian and Drucker.[32]

Ionometric measurements were made by the ionometer as described by Christiansen[33] and corrections were made for the protein content of the plasma.[34]

Phenolsulphonephthalein determinations were done by the intravenous method.

Food calculations were made by the hospital dietitian.

For composition and physical properties of human blood see Gram's article.[35]

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HYPOGLYCEMIA.

By George H. Hoxie, A.M., M.D.,

and

Gladys M. Lisherness, A.B.,

Kansas City, Mo.

The question of the existence of a chronic condition of hypoglycemia has been brought to the fore by our experiences with insulin and by the observations of such men as Seale Harris.[1]

It has seemed to us probable that some light could be thrown on the question by studying the records of routine blood sugar

tolerance tests, and, whenever a hypoglycemic condition was discovered, noting the symptomatology presented by those patients. This would, of course, demand that we establish a low limit for the normal. It would demand also that all those cases of hypoglycemia where the results are dependent on complicating circumstances (such as pylorospasm) be ruled out. And further it would require a study of the curves in order to see if the hypoglycemic curve presented the same type of curve as the normal curve.

We have, therefore, gone over our records of routine examinations and find that of 307 examinations made, there were many cases showing low blood-sugar levels, and that among these were curves that were as truly diabetic in form as among the hyperglycemics, and also (that which was for the most part present) there were strictly normal curves. We have, therefore, proceeded with the study and submit the following notations:

Method of Study. When the study of blood sugar was introduced, we used the Epstein micro method. Then as the technique was better refined, we used the picric-acid method of Benedict, and finally the technique of Folin and Wu. The results obtained by these three methods were so uniform, that we believe our records are comparable and correct.

The tests for sugar in the urine were all made with Benedict's qualitative solution.

Our routine method was to have the patient come to the office in the morning, fasting. After the urine and blood were taken, syrupy glucose was given in doses of 1.75 gm. per kilogram of body weight, made up to the quantity of 300 cc. by the addition of water and the juice of one orange. Reëxamination of the blood and urine was made at the end of a half hour, at the end of the hour, and at the end of two hours. We have found that the curve, at the end of two hours, was sufficiently definite to give us a clew as to whether it was diabetic or not. Consequently we have omitted taking the blood and urine at the third and fourth hours.

In collecting the cases for this study, we have set as the lower limit for the normal at 0.07, for the fasting condition; and the high point at 0.12, in order to eliminate those cases in which the blood-sugar level was only temporarily low, and which under ordinary conditions would rise higher.

We might say also that many, if not most, of these patients were submitted to this study, not because they were suspected of being diabetic, but in order to evaluate their endocrine balance, in particular with the study of the basal metabolic rate. In this way, we have obtained a different group than if we had studied only those who were suspected of being diabetic.

Results. Of 307 routine studies, 95 had a fasting blood sugar below 0.07, and of these 95, 50 showed a curve that did not rise above 0.12. It is worth noting that there were 23 cases that had a

blood sugar below 0.07 in which sugar appeared in the urine during the test. This may be taken as corroborative evidence of the independence of the blood sugar level from glycosuria.

As soon as we began to study the symptoms presented by this group of 50 cases, we found it wise to separate them into two subgroups—those with mental disturbances and those without. Perhaps this was unnecessary but it gave us a further subdivision of the groups. We made further a subdivision between those showing glycosuria and those not showing glycosuria. As a result, we

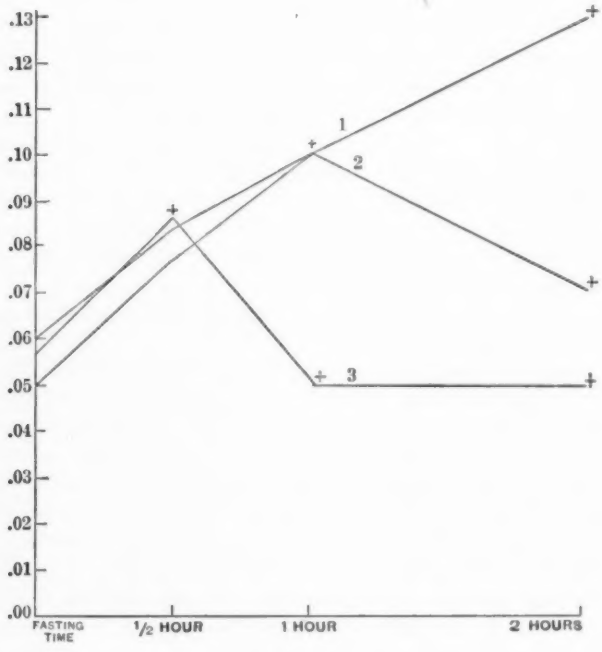

FIG. 1

divided the cases into four groups: Group I, hypoglycemia with glycosuria and showing mental disturbance; Group II, hypoglycemia with glycosuria but without distinct mental disturbance; Group III, hypoglycemia without glycosuria and without mental disturbance; Group IV, hypoglycemia without glycosuria but with mental disturbance.

Under Group I, that is, patients with hypoglycemia and glycosuria, who show distinct mental disturbance—we found only three patients who conformed to the limits of the test. These were a girl, nineteen, a woman, thirty-eight, and a woman, fifty-one years of age (Fig. 1).

The girl exhibited symptoms of duodenal ulcer but was mentally so ill-balanced that she would not take any consecutive line of treatment. At the time of first examination, her blood pressure was 80 to 122; temperature, 98.4; pulse, 88. The symptoms began with influenza in 1919 which had been followed by a cough

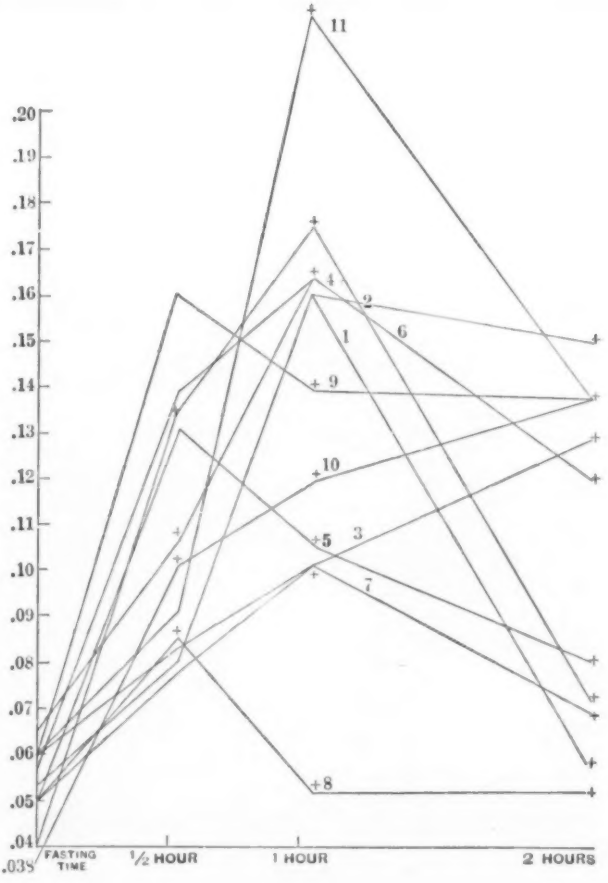

FIG. 2

with soreness of "stomach." The soreness of the abdomen kept her awake. Appetite poor. Bowels constipated. Menstruation normal. The Roentgen ray examination showed a distorted duodenum with considerable dilatation. She was jumpy both physically and mentally.

No. 2 complained chiefly of pain in the lower right abdomen, of flatulence, loose bowel action, poor appetite, poor sleep, irregular

menstruation. At the time of her first examination her blood pressure was 90 to 140; temperature, 99; pulse, 100. Her best weight had been 154 and was then 141. There was a trace of sugar in the urine. The culture of the urine showed colon bacillus infection. Her weakness was such that she could not care for her children, and was unable to see anything but the dark side of life. Nevertheless, during the period of observation she gave birth to a healthy child.

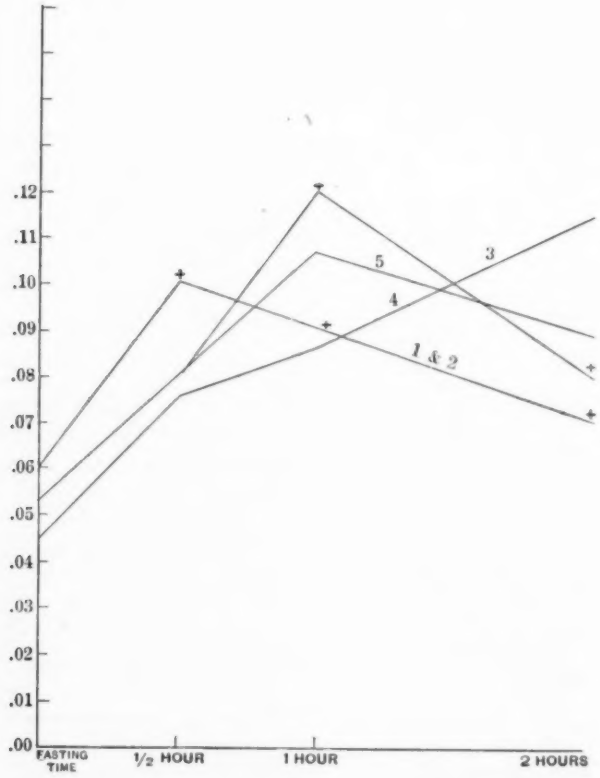

FIG. 3

No. 3 complained of various abdominal pains and nervousness. Her temperature was 99.3, pulse, 112. Best weight 180, present weight 171 pounds. The phthalein renal-function test was 41 per cent in two hours, and the urine showed occasional traces of sugar. She was particularly apprehensive and rather exaggerated every possibility of misfortune.

If we were to enlarge this group by including in it those cases wherein the blood-sugar level went high during the test, we should

have 11 cases but the symptomatology would not vary greatly from that which we have just reviewed (Fig. 2).

Under Group II, that is, those showing hypoglycemia with glycosuria but without distinct mental disturbance, we found 5 cases. No. 1, was a girl, aged nineteen years, who had been compelled to begin work for a living and became thoroughly exhausted in the struggle for existence. No. 2, was a university student who

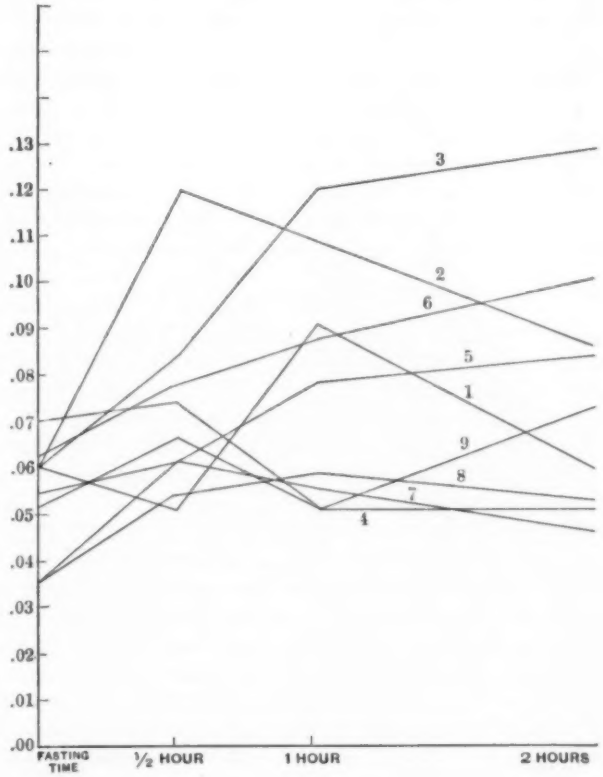

FIG. 4

had influenza followed by an inflammation apparently perisplenitic in reaction. No. 3 was a deaf man, aged thirty-five years, with Graves' disease. No. 4 was a deaf man, aged sixty years, irritable and finding it difficult to make both ends meet. No. 5 was a pregnant woman, aged thirty-nine years. The complaints of these people included sick headaches, pain in the chest, nausea and vomiting. The young girl fainted at work and suffered from cardiac palpitation (Fig. 3).

There were 9 cases in Group III, that is, hypoglycemia without glycosuria and without mental disturbance. No. 1 was that of an incipient tuberculosis in an overworked journalist; No. 2, an obese nurse; No. 3, a young woman with incipient tuberculosis; No. 4, an overworked musician; No. 5, a teacher with chronic arthritis; No. 6, an overworked young law student; No. 7, an overworked librarian; No. 8, was a bank teller who had influenza one year

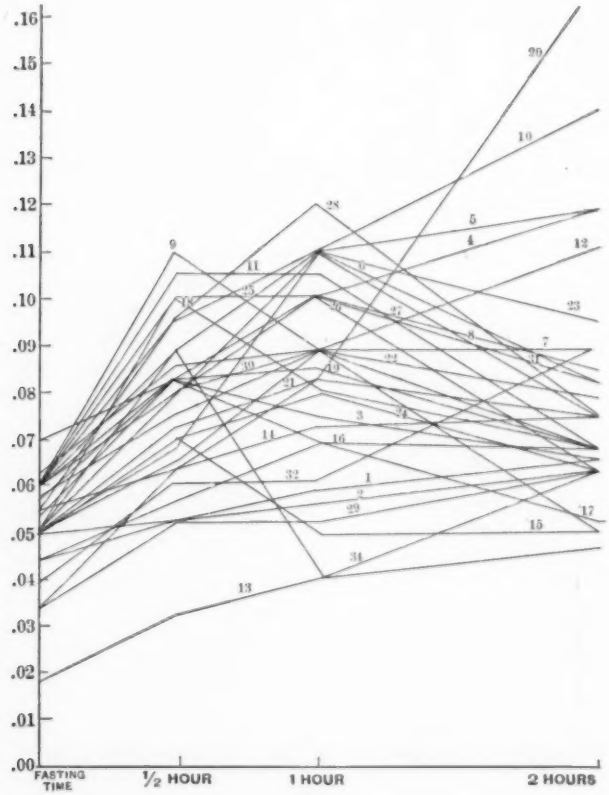

FIG. 5

previous; No. 9 was an overworked Y. W. C. A. secretary. The general symptoms were fatigue, nervousness, depression, and in the young women, attacks of weeping and the general complaint of dysmenorrhea (Fig. 4).

There were 33 cases in Group IV, that is, hypoglycemia without glycosuria but with some mental upset. They might all be grouped under the head of constitutional inferiority, or, again, the disciple of Freud would find in them all sorts of complexes. Here again

there was among the women the complaint of irregular menstruation, backache, headache, fatigue, lack of endurance and even of abdominal pain. The males complained chiefly of inability to keep up with their fellows in one or more particulars, with the exception of a boy, aged fourteen years, who had distinct epileptiform attacks (Fig. 5).

Comment. The perusal of these sketchy notes on the case histories hardly leaves the reader with an adequate idea of the conditions involved or the symptoms presented, therefore we think that it may be worth while to give our own opinion as to the significance of this group of cases.

There is apparently a condition in which the blood stream contains an amount of sugar less than that spoken of as normal. This condition can exist for considerable time, that is, become chronic. Furthermore this condition seems to be accompanied by nervous and mental disturbances very much akin to those presented by the initial symptoms of acute hyperinsulinism or hypoglycemia.

As far as one could judge from the study of these cases the cause does not lie in a lesion of the pancreas, rather it seems to lie in a general depression of the metabolism of the body.

But it is not clear from these case histories whether the hypoglycemia is the cause of the nervous disturbance or *vice versa*. But since we have noticed that the hypoglycemia tends to disappear as soon as the general nutrition of the patient improves, we have been led to think that the hypoglycemia is a result of the general nervous state rather than the cause of it.

If we accept the opinion of Falta and others that in disordered sugar metabolism and diabetes there is involved more than a lesion of the pancreas—that there is a disorganization of the vegetative nervous system—then it is easy to understand that in our cases the hypoglycemia may result from a disorganization of the nervous system rather than from any lesion of the pancreas or from hyperinsulinism. Furthermore, as far as we can ascertain from a perusal of these histories the metabolism seems to be slowed down rather than stimulated. In other words, it is not hyperinsulinism so much as a lowered sugar metabolism.

This study emphasizes again the mutual independence of glycosuria and the blood-sugar level. A glance at the curves show the percentage of diabetic curves is about that which one would expect from an unselected run of office cases.

The underlying cause of the condition seems to have been overwork, debilitating disease (such as influenza), and worries. In other words, some type of exhaustion. Focal infection was, of course, occasionally present; but focal infection is just one of the causes of systemic exhaustion.

The effect of treatment in this group of cases is marked. We have been able to watch the blood-sugar reaction in several of the

cases listed in this communication and have found that with the returning strength the blood sugar returned to its normal limits. This usually occurs in from three to six months. This result would indicate that the theory that this hypoglycemia reaction is due to exhaustion is the correct one.

As to the type of treatment we have found that arsenic, introduced in the form of arsacetin or even of the cacodylates, or occasionally in the form of silver-salvarsan has been most effective. This was of course combined with synergistic symptomatic treatment.

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A CONFIRMATORY SIGN FOR THE DIAGNOSIS OF OTITIS MEDIA ASSOCIATED WITH PULMONARY TUBERCULOSIS.

By Nicholas Michelson, M.D.,

AND

Morris M. Weiss, M.D.,

NEW YORK.

(From the Montefiore Hospital, Bedford Sanatorium, Bedford Hills, N. Y.)

Patients with pulmonary tuberculosis who have otitis media are able to perceive with the diseased ear, sounds originating in their respiratory tract. They are oftened puzzled over this apparent paradoxical phenomenon of hearing only with their "deaf" ear such intrathoracic sounds as rales, rhonchi and squeaks. These sounds can be differentiated by oral auscultation from the subjective sensations of buzzing, ringing or pulsations, usually complained of in otitis media. In every instance of otitis media rales originating in the tuberculous lung, when detected by the examiner orally, were also heard by the diseased ear, and when such oral auscultation was negative no rales were heard by the patient.

We can utilize this clinical picture as a confirmatory sign in the diagnosis of otitis media in phthisical patients. We believe it is important in such cases and should be used along with the routine otologic tests. In every instance it was confirmed by the Weber, Schwabach, Rinné and whispered-voice tests. It indicated the presence of an involvement of the sound-conducting mechanism of the diseased ear and served to differentiate such disturbance from nerve deafness.

The following cases illustrate its diagnostic value:

Case I.—(No. 8350.) A man, aged forty years, in November, 1924, had a spontaneous discharge from the right ear, without pain

or fever but with concomitant loss of hearing. The discharge lasted about six months. Since then there has been a constant ringing in this ear. For the past year he has also heard with the right ear a crackling, clicking sound which comes from his throat and chest only when he breathes, both on inspiration and expiration.

Otologic examination showed a central perforation of right tympanic membrane, but no discharge.

Hearing tests: (*a*) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine and so forth) heard at a distance of 1½ inches; high-pitched words (six, seven and so forth) heard at a distance of 2 inches.

(*b*) Weber: Right: Tuning fork C (128 vibrations per second), positive.

(*c*) Schwabach: Right: Tuning fork C, positive ten seconds.

(*d*) Rinné: Right: Tuning fork C, negative twelve seconds; C^1 (256), negative ten seconds; C^2 (512), negative twenty seconds; C^3 (1024), negative twelve seconds.

Diagnosis: Right chronic otitis media sicca.

Oral auscultation: Constant, large, moist rales.

Physical examination of the lungs: Fibroulcerative tuberculosis involving the entire left side and the right upper lobe with scattered infiltrations throughout the right middle and lower lobes. There is a large cavity in the right upper lobe and a small cavity in the left upper lobe. Numerous large and small moist rales are heard over both lung fields.

CASE II.—(No. 8173.) A man, aged twenty-one years, in May, 1924, had a "cold in the head." He felt a slight pain in his right ear associated with a ringing sound. Three days later he noticed a yellowish-brown discharge from this ear which persisted. The hearing gradually decreased. His diseased ear now conveys the sensation of clicking and rasping sounds which originate in his throat and chest. These superimposed sounds are only present when the patient breathes.

Otologic examination showed destruction of the entire right tympanic membrane, with a thin, purulent discharge.

Hearing tests: (*a*) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine, and so forth) heard at a distance of 5 to 7 inches; high-pitched words (six, seven and so forth) heard at at a distance of 11 feet.

(*b*) Weber: Right: Tuning fork C, positive.

(*c*) Schwabach: Right: Tuning fork C, positive eight seconds.

(*d*) Rinné: Right: Tuning fork C, negative fourteen seconds; C^1, negative ten seconds; C^2, negative twelve seconds; C^3, negative fifteen seconds.

Diagnosis: Right chronic purulent otitis media.

Oral auscultation: Constant, large, moist rales.

Physical examination of lungs: Bilateral fibroulcerative tuberculosis with a large cavity in the left upper lobe and a small cavity in the right upper lobe. Large constant moist rales over both upper lobes.

CASE III.—(No. 8350.) A man, aged twenty-seven years, in January, 1925, had severe pains in the left ear which radiated to his head. This pain subsided five weeks later, when a thin yellowish discharge appeared. The hearing was lost at this time. The discharge has been continuous. He has a constant ringing and buzzing in this ear; but during the past few months on inspiration only, he also hears a faint clicking sound which comes from his throat and chest.

Otologic examination showed destruction of three-fourths of the tympanic membrane of the left ear, with a thin, purulent discharge.

Hearing tests: (*a*) Whispered voice: Right: Normal. Left: Low-pitched words (five, nine and so forth), no perception; high-pitched words (six, seven and so forth) heard at a distance of 3 inches.

(*b*) Weber: Left: Tuning fork C, positive.

(*c*) Schwabach: Left: Tuning fork C, positive eleven seconds.

(*d*) Rinné: Left: Tuning fork C, negative twenty-seven seconds (no air conduction); C^1, negative sixteen seconds (no air conduction); C^2, negative forty seconds; C^3, negative twenty-eight seconds.

Diagnosis: Left chronic purulent otitis media.

Oral auscultation: Distant, small, moist rales.

Physical examination of lungs: Fibroulcerative tuberculosis of both upper lobes. Numerous constant large and small moist rales in these areas.

The next case is cited as a contrast:

CASE IV.—(No. 8294.) A man, aged twenty years, about 1918, had a thin, yellowish discharge from the right ear associated with no pain or impairment of hearing. The patient did not consider himself sick at that time. The discharge ceased after a year. In March, 1926, the right ear again began to discharge, soon followed by impairment of hearing without pain. He has a constant ringing sensation in the diseased ear, but hears no sounds emanating from throat or chest.

Otologic examination showed that the upper and lower anterior quadrants of the right tympanic membrane were destroyed, with a thin purulent discharge.

Hearing tests: (*a*) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine and so forth) heard at a distance of $1\frac{1}{2}$ inches; high-pitched words (six, seven and so forth) heard at a distance of 2 feet.

(*b*) Weber: Right: Tuning fork C, positive.

(*c*) Schwabach: Right: Tuning fork C, positive twenty seconds.

(*d*) Rinné: Right: Tuning fork C, negative twenty-five seconds; C^1, negative twelve seconds; C^2, negative thirty-six seconds; C^3, negative fifteen seconds.

Diagnosis: Right chronic purulent otitis media.

Oral auscultation: Negative.

Physical examination of lungs: Fibroulcerative tuberculosis of right upper and middle lobes with small cavity in left upper lobe. Numerous fine, constant, moist rales over these areas.

The following case demonstrates the differential diagnostic significance:

CASE V.—(No. 7734.) A man, aged twenty-seven years, claims that he was born deaf. He has an occasional "ringing" sensation in his ears, but hears no sounds from his throat or chest.

Otologic examination showed a retraction of both tympanic membranes. The left is atrophic and transparent. The manubrium mallei and the promontorium are distinctly visible.

Hearing tests: Rinné: Positive. The only tone perceived was C^4 by air conduction: Ten seconds on the right and twelve seconds on the left.

Diagnosis: Congenital acoustic nerve disease.

Oral auscultation: Constant, large, bubbling rales.

Physical examination of lungs: Bilateral fibrocavernous tuberculous lesion of upper lobes with ulcerative process throughout the left lower lobe. Large, constant moist rales.

Summary. The first 3 cases present unilateral chronic purulent otitis media. In each instance the rales heard over the diseased lung were audible by oral auscultation as well. The patient heard these rales only with the diseased ear. The fourth case also shows a chronic purulent otitis media. The rales present in the chest were not heard by oral examination nor were they heard by the patient. The fifth patient has congenital nerve deafness. Bubbling rales heard orally and by thoracic examination were not heard by the patient.

What is the mechanism of transmission and perception of these rales? In otitis media, as is well known, there is impaired air conduction and intensified bone conduction on the diseased side. In the first 3 cases cited the rales detected by oral auscultation were conveyed from the lung to the trachea. From here they were transmitted to the bones of the head, and because of the better bone conduction were heard by the diseased ear. In Case IV there was no transmission of the rales from the lungs to the oral cavity and hence they could not be appreciated by the patient. In the

case of the nerve deafness, while the rales were conveyed to the oral cavity and to the cranial bones, they were not perceived by the patient because in nerve deafness there is a lack of nerve response to most sound waves; only a few extremely loud tones can be heard.

Conclusions. Tuberculous patients with otitis media often can hear their pulmonary rales with their diseased ear. This audition of pathologic sounds serves to differentiate otitis media from acoustic nerve involvement.

THE EFFECT OF BISMUTH ALONE AND IN COMBINATION WITH THE ARSENOBENZENES ON THE WASSERMANN REACTION.[1]

By Carroll S. Wright, M.D.,

ASSOCIATE PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY IN THE POST-GRADUATE SCHOOL OF THE UNIVERSITY OF PENNSYLVANIA.

That bismuth exerts a favorable action on the course of syphilis is well known and generally accepted at the present date. Given intramuscularly its action is equal to if not superior to that of mercury and the day is approaching when bismuth will perhaps largely replace mercury in the treatment of syphilis, as it is therapeutically stronger, less painful and less toxic.

The day of sole dependence on the arsenobenzenes has passed. With but few exceptions, syphilographers now agree that adjunctive treatment is not only desirable but is imperative. It is the writer's purpose in this paper to indicate the value of bismuth as an adjunct to the arsenobenzenes.

Before 1922 it was the custom in the syphilis clinic of the Polyclinic Hospital in Philadelphia,[2] to treat all stages of syphilis with long courses of neoarsphenamin, mercury being reserved for such cases as were intolerant or resistant to the arsenobenzenes, and for short rest periods. With the introduction of bismuth this procedure was changed and treatment by means of alternate courses of neoarsphenamin and bismuth was instituted in new cases and to those patients who had had a considerable amount of arsenobenzen treatment previously, bismuth alone was given. Since 1923, the writer has personally administered the intramuscular treatment to over 200 cases, in all giving between 4000 and 5000 injections of the drug. Of these cases, 160 received a sufficient amount of treatment to enable the drawing of some conclusions as to the

[1] Potassium bismuth tartrate furnished by the Dermatological Research Laboratories.

[2] Clinic of Prof. Jay F. Schamberg.

effectiveness of the treatment. Courses of injections were given, 16 injections being the usual number for a course but in some instances as many as 30 or 40 consecutive treatments were administered, at weekly intervals. Potassium bismuth tartrate was used in doses of 100 mg. each week. This dose was decided upon because it kept the patient just at the saturation point, as evidenced by the presence of a blue line on the gums after three or four weeks of treatment.

Potassium Bismuth Tartrate as an Adjunct to Neoarsphenamin in Secondary Syphilis. Owing to the segregation of cases of secondary syphilis in the clinic for other therapeutic research, only 10 cases have received the usual neoarsphenamin followed by bismuth. It was formerly a routine in the clinic to give from 10 to 20 injections of neoarsphenamin for the first course of treatment of secondary syphilis, the average dose being 0.6 gm. weekly for women and 0.9 gm. for men. After a short rest period, neoarsphenamin was again given. Thus it will be noticed in Table I that one patient received as many as 50 injections of neoarsphenamin before bismuth was given. It is of further interest that this patient was still serologically positive after this number of injections and became Wassermann negative after 18 injections of bismuth or a total of 1.8 gm. of the drug. Of the 10 cases in this series, 6 were serologically negative after an average of 11 injections of neoarsphenamin. All of these have remained persistently negative under further intramuscular injections of bismuth. Each of the 4 cases which were still Wassermann positive after the first course of neoarsphenamin, became negative after an average of 10 injections of bismuth, and to date have remained persistently negative.

Bismuth as an Adjunct to Neoarsphenamin in the Treatment of Secondary Syphilis. In all, 75 cases of syphilis having no other symptoms than a positive blood Wassermann reaction received a sufficient amount of bismuth to draw some conclusions as to its value. Of these 75 cases, only 18 (or 22.5 per cent), were serologically negative after an average treatment of 17 injections of neoarsphenamin and 7 injections of mercury (insoluble). With the institution of bismuth there remained 57 cases having a positive blood Wassermann. Of these 57 cases, 32 (or 51 per cent) became serologically negative after an average of 13 injections of bismuth. It is interesting to note that all of the 18 cases which were Wassermann negative after treatment with neoarsphenamin and mercury have remained negative under subsequent bismuth therapy. Of the 32 cases which became negative after the institution of bismuth all but 5 have remained serologically negative. The 5 cases which again became Wassermann positive took self-advised rest periods varying from several months to a year, during which time they received no treatment at all.

TABLE I.—SECONDARY SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Neoarsphenamin, doses.	Wassermann after neoarsphenamin.	Bismuth, doses.	Wassermann after bismuth.	Wassermann reaction became negative.
M. Br.	16	Neg.	16	Neg.	After 9 injections neoarsphenamin.
M. Bo.	50	4+	44	Neg.	After 18 injections bismuth.
B. D.	16	Neg.	16	Neg.	After 7 injections neoarsphenamin.
M. F.	18	4+	38	Neg.	After 10 injections bismuth.
J. K.	10	4+	28	Neg.	After 6 injections bismuth.
C. K.	10	4+	43	Neg.	After 8 injections bismuth.
M. M.	14	Neg.	14	Neg.	After 9 injections neoarsphenamin.
A. M.	20	Neg.	43	Neg.	After 18 injections neoarsphenamin.
F. L.	18	Neg.	22	Neg.	After 16 injections neoarsphenamin.
D. S.	18	Neg.	60	Neg.	After 10 injections neoarsphenamin.

Certain cases in this group are of particular interest:

CASE I.—A. C., female, colored, aged thirty years, presented no symptoms of syphilis other than a positive Wassermann reaction, and received a total of 28 injections of neoarsphenamin (average dose, 0.6 gm. weekly) over a period of one and a half years. At the end of that time the Wassermann reaction was negative. After a short rest period, the Wassermann was again strongly positive. Bismuth was then started and after 6 injections of 100 mg. each of the drug, the blood Wassermann was again negative and has remained so for two years during which time the patient has had two healthy nonsyphilitic children.

CASE II.—G. G., female, white, aged twenty-eight years, presenting no signs or symptoms of syphilis other than a strongly positive Wassermann reaction, received 16 injections of neoarsphenamin after which the Wassermann was still strongly positive. After 14 injections of bismuth (100 mg. each) the Wassermann reaction was negative. Treatment with neoarsphenamin was then again instituted and while receiving this drug the blood Wassermann again became positive. She is now receiving bismuth again.

CASE III.—G. W., colored, male, aged twenty-eight years, with no evidence of syphilis other than a strongly positive Wassermann reaction, received 20 injections of neoarsphenamin (average dose, 7.5 gr. weekly), then 14 injections of 2 gr. each of the mercury salicylate intramuscularly. This was followed by a second course

of neoarsphenamin consisting of 20 injections. After all of this treatment, the Wassermann reaction was still strongly positive. Bismuth was then instituted and 16 injections of the drug have reduced the Wassermann reaction to negative.

Use of Potassium Bismuth Tartrate as Adjunctive Treatment in Tertiary Syphilis. It is well known that it is extremely difficult to influence the Wassermann reaction in cases of cutaneous, visceral or nervous system tertiary syphilis with any kind or amount of therapy. Including all these three types, 27 cases of tertiary syphilis were treated, all of which were serologically positive in the beginning and only 2 of which were negative at the start of bismuth therapy. After an average of 16 injections of bismuth, 7 of the 25 still Wassermann positive cases were serologically negative. Four of these later reverted to positive. In these cases bismuth apparently does not exert a more favorable influence upon the blood Wassermann than do other antisyphilitic remedies.

Use of Bismuth in Congenital Syphilis as Adjunctive Treatment to Neoarsphenamin and Mercury. Upon the suggestion of Dr. Schamberg, a number of cases of secondary and latent syphilis were treated with alternate injections of neoarsphenamin and bismuth, one injection of each drug being given in the same week, at intervals of three days, the usual doses being employed. The efficacy of this therapeutic procedure may be ascertained by a study of Tables II and VI.

1. *Secondary Syphilis.* In all, 13 cases of secondary syphilis have been treated in this manner to date. All of these were serologically negative before the completion of the first series of injections covering a period of twelve weeks. The average number of weeks required to obtain negative serologic reactions was six. In 1 case, a colored girl with a maculopapular eruption and rectal condylomata, the Wassermann reaction was negative after three weeks. In secondary syphilis treated in this way it has been customary to give first an injection of 100 mg. of potassium tartrobismuthate, in order to avoid the danger of a Herxheimer reaction, or toxic reaction so often caused by initial injection of neoarsphenamin intravenously. So successful was this treatment in this number of cases that it is advised for all cases of early syphilis. It is of further importance that in not one of these cases reported has the Wassermann reaction reverted to a positive. The effect upon the local manifestations of syphilis is magical. Under the combined influence of bismuth and neoarsphenamin cutaneous lesions disappear with astonishing rapidity.

TABLE II.—TERTIARY SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Diagnosis.	Previous therapy.		Wassermann at start of bismuth.	Doses of bismuth to date.	Doses of bismuth for negative Wassermann.	Wassermann not affected.
		Neoarsphenamin, doses.	Mercury, doses.				
M. B.	Aortitis	9	?	4+	28	...	Wk. pos.
C. B.	Gummata	25	8	Wk. pos.	20	12	
L. B.	Tabes	...	...	Wk. pos.	40	12	
E. B.	Tabes	...	....	4+	30	...	+
H. B.	Tabes	128	32	4+	28	24	
P. C.	Tabes	10	...	4+	32	...	+
H. C.	Gumma	...	...	4+	24	...	+
I. C.	C.S.S.	35	16	4+	75	...	+
A. C.	Tabes	38	9	4+	10	...	+
M. F.	Gumma	51	18	4+	45	...	+
A. F.	Gumma	20	...	4+	53	16	
W. F.	Gumma	28	14	4+	30	19	
C. G.	C.S.S.	8	...	4+	36	...	+
M. H.	Gumma	12	...	Neg.	24	...*	
M. K.	Gumma	30	?	4+	33	...	+
E. H.	Gumma	24	10	4+	12	...	+
E. M.	C.S.S.	2	...	2+	71	16	
I. P.	Gumma	...	...	...	14	...	+
A. P.	Gumma	18	...	4+	22	...	+
U. P.	Gumma	...	...	4+	16	16	
B. R.	Tabes	13	...	4+	20	...	+
M. S.	Optic atrophy	...	...	4+	28	...	+
C. S.	Optic atrophy	20	12	4+	34	...	+
P. T.	C.S.S.	17	6	4+	26	...	+
H. T.	Aneurysm	26	11	Neg.	30	...*	
H. V.	Tabes	52	17	4+	40	...	+
C. W.	C.S.S.	16	...	4+	26	...	+

* Wassermann persistently negative.

TABLE III.—CONGENITAL SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Other therapy.		Wassermann at start of bismuth.	Doses of bismuth to date	Doses of bismuth to render Wassermann negative.	Uninfluenced.
	Neoarsphenamin.	Bismuth.				
M. B.	40	18	4+	60	27	
B. B.	12	...	4+	50	20	
A. B.	...	...	Mod. pos.	25	...	+
I. B.	16	...	4+	40	...	+
G. C.	30	9	4+	20	...	+
V. C.	51	13	4+	45	...	+
R. D.	38	16	4+	60	16	
H. D.	15	...	4+	30	28	
M. G.	51	16	4+	45	...	+
H. G.	16	...	4+	44	7	
A. H.	17	...	2+	12	12	
E. K.	50	22	4+	50	88	
F. M.	8	...	4+	30	18	
E. M.	38	14	4+	63	...	+
S. P.	21	...	4+	28	...	+
B. V.	...	...	4+	28	18	

TABLE IV.—SECONDARY SYPHILIS TREATED WITH ONE INJECTION OF NEOARSPHENAMIN AND ONE INJECTION OF BISMUTH WEEKLY.

Name.	Eruption.	Weeks to obtain negative Wassermann.	Remarks.
E. B.	Maculopapular condylomas	3	Rapid disappearance of lesions.
A. D.	Papular, moist papules	9	
R. M.	Maculopapular	4	Has remained negative under further bismuth therapy.
M. J.	Roseola, moist papules	12	No Wassermann taken until completion of the first course.
L. M.	Maculopapular	8	Has remained negative under further bismuth therapy.
G. S.	Maculopapular	6	Has remained persistently negative under further bismuth therapy.
W. S.	Maculopapular	5	Has remained negative under further bismuth therapy.
B. E.	Roseola	9	Has remained negative.
C. M.	Maculopapular	4	Still negative some months later; disappeared then from clinic.
H. W.	Maculopapular	5	Rapid involutions of the eruption.
D. W.	Maculopapular moist papules	5	Has remained persistently negative.
P. T.	Maculopapular	5	Has remained persistently negative.
D. W.	Maculopapular	...	Has remained persistently negative.
Dr. M.	Roseola	6	Has remained persistently negative.

TABLE V.—LATENT SYPHILIS TREATED WITH ONE INJECTION OF NEOARSPHENAMIN AND ONE INJECTION OF BISMUTH WEEKLY.

Name.	Wassermann.	Weeks to obtain a negative.	Wassermann reverted to positive.	Wassermann uninfluenced.
N. B.	4+	5	+	
P. B.	2+	7		
G. D.	4+	...	...	+
N. C.	4+	5		
A. E.	4+	9		
A. L.	1+	6		
A. M.	4+	12		
M. F.	4+	6		
B. J.	4+	12	+	
M. R.	4+	5		
J. G.	4+	8		
G. W.	4+	...	...	+
W. W.	4+	...	...	+
M. W.	4+	8		
J. W.	4+	5		
R. W.	4+	...	...	+
M. P.	4+	6		
J. M.	4+	6	+	

TABLE VI.—SUMMARY OF RESULTS.

	Diagnosis.					
	Secondary lues.	Latent lues.	Tertiary lues, cutaneous	Tertiary C. S. S. lues.	Secondary visceral lues.	Hereditary lues.
Number of cases	9	75	11	14	3	16
Neoarsphenamin doses, average	19	17	19	20	12	18
Mercury doses, average	..	7	5	9	6	8
Wassermann negative after above	6	18	1	..	1	
After above, per cent negative	60	22.5	9	..	33	
Remaining negative under bismuth, per cent	100	100	100	..	100	
Cases positive at start of bismuth	4	57	10	14	2	16
Negative after bismuth	4	32	4	3	..	9
Made negative by bismuth, per cent	100	51	40	20	..	56
Injections of bismuth to obtain negative Wassermann, average	10	13	16	17	..	17
Cases reverting to positive	..	5	2	2	..	1
Cases unaffected by all therapy	..	23	6	11	2	7

2. *Latent Syphilis.* The effect of this combined intensive therapy is but little less striking when used in the treatment of latent syphilis. Of 18 cases treated, 14 became serologically negative in an average of 7 doses. As to the persistence of the negative Wassermann reaction in these cases, I am unable to draw conclusions for the time has been too short. Six of the patients disappeared from the clinic after obtaining negative blood reports. Two of these were brought back after several months and were found to be again serologically positive. A third case reverted to a positive after a short rest. The remaining 7 negative cases have remained persistently negative to date under further treatment with bismuth alone. Comparing the effects of this intensive method of treatment with the results obtained by the use of alternate courses of neoarsphenamin and bismuth or neoarsphenamin and mercury, the first named is strikingly superior. It is of extreme importance that none of these cases developed albuminuria at any time in spite of the intensity of the treatment.

The rationale of giving one injection of an arsenobenzene and one injection of bismuth in the same week is obvious. In the arsenobenzenes we have direct spirocheticides, whose action though powerful is of short duration; in bismuth we have a drug, which though spirocheticidal to a less degree, probably has the effect of stimulating natural resistance on the part of the tissues and which being absorbed daily in small amounts continually bombards the infection.

There are no rest periods which permit the reëstablishment of spirochetal foci. The use of mercury in the same way has been decried because of its greater tendency to damage the kidneys and thus interfere with the free elimination of arsenic.

Benignity of Bismuth. Aside from its powerful action in all stages of syphilis, bismuth deserves especial recognition because of its low toxicity. In three years the writer has never observed stomatitis of a sufficient degree to warrant discontinuation of the drug, and this is the more remarkable in view of the fact that the majority of the patients treated in this clinic are of a class that pay but scant attention to buccal hygiene. It is customary for a blue line of greater or lesser intensity to develop on the gum margin after a total of from 300 to 500 mg. of potassium bismuth tartrate intramuscularly, but this offers no contraindication to its continuance. Foul breath is also common.

Just how many of the 40 or 50 odd cases that discontinued treatment did so because of local pain produced, it is difficult to say. In 7 instances, patients reported to the writer that they were unable to continue injections because of the local pain. Many patients reported that they preferred the intramuscular injections to intravenous injections.

Occasionally nodes would develop, but these quickly disappeared under local massage and hot applications. One of the most frequent symptoms complained of was that of muscular weakness developing a day after the injection and persisting for several days. The cause of this is unknown.

Eczematoid eruptions developing during the course of bismuth therapy were observed in 5 cases, and close study of these cases suggested very strongly that the eruptions were actually due to the bismuth.

Albuminuria was exceedingly uncommon, occurring in only 4 cases and then only faint traces of albumin being observed in the urine. A number of patients showing more or less marked albuminuria while receiving neoarsphenamin remained free of albumin while receiving bismuth.

The rarity of untoward symptoms may be partially explained by the fact that the author used smaller doses of bismuth than are employed in France where bismuth was first used in the treatment of syphilis.

Comment. The results obtained in these cases would indicate that bismuth deserves a high ranking among antisyphilitic remedies because of its ability to favorably influence the Wassermann reaction and because of its low toxicity. Other writers, and many of them, have shown the specificity of bismuth *per se* in the presence of active syphilis of all types.

Oftentimes the Wassermann reaction will become negative some weeks or months after the cessation of all antisyphilitic therapy

and it is possible that a certain per centage of the cases in this series which were still positive after receiving a considerable amount of neoarsphenamin would have become serologically negative had the bismuth not been used. However the majority of these patients had been under observation for a considerable length of time and had had rest periods without this occurring.

The majority of patients under treatment in our syphilis clinic at the present date are cases in which it is not desirous to employ the organic arsenicals, and indeed it would appear that the organic arsenicals are woefully lacking in ability to reduce the positive Wassermann reactions to negatives except in very early cases of syphilis. The value of bismuth is becoming more and more evident. Given in early syphilis its spirocheticidal activity is but little less than that of the arsenobenzenes and yet it does not provoke the severe reactions that are not uncommon following the initial dose of an arsenobenzene. Therefore it is an excellent drug to give at the start of the treatment of primary and secondary syphilis. Because of its action in reducing positive Wassermann reactions to negatives in a large percentage of cases of syphilis it is an excellent drug to be administered in cases of latent syphilis or socalled Wassermann-fast syphilis. Because of its low toxicity and painlessness as compared with mercurial salts administered in the same way, it is the drug of choice as a synergist to the arsenobenzenes.

Summary. In this study of the action of bismuth as a synergist to neoarsphenamin in all stages of syphilis, 160 cases are reported. In 128 of these cases the bismuth was given after the patient had already received one or several courses of neoarsphenamin and in some instances a few injections of mercury. Only 26 cases out of these 128 (or approximately 20 per cent) were Wassermann negative after an average of 18 injections of neoarsphenamin and 6 injections of mercury salicylate. Of the 102 cases still Wassermann positive, 52 (or 51 per cent) were serologically negative after an average of 15 injections of 100 mg. each of bismuth, given intramuscularly. Of this number, 5 cases of latent syphilis, 4 cases of tertiary syphilis and 1 case of congenital syphilis reverted again to a positive at a later date.

One of the most important facts disclosed by this study is that, of the cases which were serologically negative after treatment with neoarsphenamin and mercury, every one remained persistently negative upon the continuation of the treatment with intramuscular injections of bismuth. With this knowledge one may feel reasonably safe, once having obtained a negative Wassermann reaction in early syphilis, in continuing the treatment with intramuscular injections of bismuth in small doses, thus avoiding the dangers of too much arsenical therapy.

Administering each week one injection of bismuth intramuscularly and one injection of neoarsphenamin intravenously proved highly

successful in the treatment of early syphilis and latent syphilis. In secondary syphilis the cutaneous manifestations disappeared with astonishing rapidity and the blood Wassermann reactions were reduced from strong positives to negatives in an average of six weeks. This negative result has been persistent to date in all cases. In latent syphilis, 14 to 18 cases treated became negative in an average of seven weeks, but four of these were again positive at a later date.

SEROLOGIC STUDIES OF PROTEINURIAS.

Results of Precipitin Tests for Specific Human Blood Protein in 100 Cases at the Salt Lake County General Hospital.*

By Ralph M. Tandowsky, M.D.,

SALT LAKE CITY.

(From the Physiological Laboratory, University of Utah, and the Salt Lake County General Hospital.)

In spite of the fact that serum albumin is the most common protein in the urine in pathologic states, we quite commonly find other proteins such as serum globulin, hemoglobin, albumose, fibrin, peptones and a large series of foreign proteins. The etiology of these proteins may result from the destruction or filtration of body proteins or the filtration of induced proteins. It may be of vast significance in some cases to determine whether the protein found in the urine is derived from the blood stream or whether it originates elsewhere.

Many writers have attempted to account for the abnormal presence of urinary proteins. Granger Stewart[1] showed that albumin in the urine may be accounted for by epithelium and other débris. Ott[2] has shown that nucleoprotein may be present in healthy urines. Almost every method of protein identification has been applied to some extent in the past. Cramer,[3] in 1908, noted that the injection of egg white and ox serum into the dog produced coagulable protein in the urine. Condorelli[4] has shown that proteins may be isolated from the urine which are not coagulable by heat or acetic acid.

The proteins in the urine which give a positive chemical test for albumin have not been completely classified serologically, and those proteins which fail to give a chemical test in the urine have been ignored.

A great amount of work has been done on the chemical and serologic detection of proteins introduced both enterally and parenterally.

* Read before Salt Lake County Medical Society, January 11, 1926.

Hamburger,[5] Michaelis and Oppenheimer,[6] Friedenwald and Isaac[7] and others have been identified with the serologic protein tests for many years. They, however, limited the greater part of their work to protein detection in the blood of the human or animal tested. Furthermore, like the majority of authors, they have spent most of their time isolating foreign proteins. Very little work appears on the detection of specific hemic proteins in the urine serologically. The writer has been particularly interested in the specific detection of protein in the urine.[8]

The close observation of mild and transient proteinurias occurring so frequently in cases entering a general hospital made a specific precipitin study of these urines seem worth while. This brief study of 100 cases is an attempt to determine the presence of hemic proteins in the urine of patients coming under my observation at the Salt Lake County General Hospital. The writer chose the detection of blood proteins in the urine for the following reasons: (1) The frequency with which leukocytes and red blood cells are found in the urine. (2) Infection is almost always accompanied by a fight between the bacteria and the blood cells, with the resultant disintegration of some of the blood. Dochez and Avery were able to detect precipitin in the urine of patients suffering with pneumonia.[9] (3) Destruction of blood cells is a constant physiologic process in healthy individuals. (4) Blood protein cannot at all times be utilized by human organisms, especially after injury, operative procedure or hemorrhage.

A hundred cases of varied diagnoses were chosen at random. Forty per cent of these gave a positive chemical urinary protein test. The majority of these positive tests, however, presented protein in amounts varying qualitatively from a very faint trace to a definite trace. Some of these proteinurias were classed as nephritic while other were ignored so far as clinical observation was concerned. Whether ignored or used as an aid in diagnosis, we cannot consider the results obtained by chemical urinary protein tests accurate for diagnostic purposes in all cases, for they fail to take into consideration the following states in which protein may be found in the urine: (1) Postoperative proteinuria; (2) postpuerperal proteinuria; (3) alimentary proteinuria; (4) orthostatic proteinuria; (5) postfebrile proteinuria.

In these types of proteinurias where definite evidence of nephritis is lacking, a specific test to determine the etiology of the protein seems indicated.

The technique of the precipitin test was as follows: A healthy rabbit was inoculated daily with increasing doses of fresh human whole blood until its serum titer became high (1 to 60,000). The rabbit was then bled by cardial puncture. The serum was separated and used immediately in the precipitin tests. To 3 cc. of filtered urine 0.2 cc. to 0.5 cc. of the antihuman rabbit serum was added at room temperature. Readings were taken within one hour of

TABULATION OF BLOOD—URINE PRECIPITIN REACTIONS.

Diagnosis.	No. cases.	Control urine.	0	±	±	+	++	+++	Nitric acid test.		Acetic acid test.		Negative (%).	Positive (%).
									+	0	+	0		
Pulmonary tuberculosis	24	Clear except tuberc. kidney	14	5	0	3	0	2	7	17	9	15	60	40
Scarlet fever	1	Clear	0	1	0	0	0	0	1	0	1	0	0	100
Acute endocarditis	1	Clear	0	0	1	0	0	0	1	0	1	0	0	100
Pregnancy	8	Clear	2	1	0	2	3	0	6	2	6	2	27	73
Acute nephritis	1	Slight cloudiness	0	0	0	0	1	0	1	0	1	0	0	100
Diphtheria	4	Clear	2	0	1	0	1	0	2	2	2	2	50	50
Chronic arthritis	2	Clear	0	0	0	1	1	0	1	1	1	1	0	100
Bronchitis	2	Clear	1	1	0	0	0	0	0	2	0	2	50	50
Typhoid fever	2	Clear	1	1	0	0	0	0	1	1	1	1	50	50
Inoperable gastric carcinoma	1	Clear	1	0	0	0	0	0	1	0	1	0	100	0
Bronchial asthma	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Tabes dorsalis	2	Clear	0	1	1	0	0	0	2	0	2	0	0	100
Cerebral hemorrhage	2	Clear	1	0	0	1	0	0	1	1	1	1	50	50
Attempted suicide	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Neuritis	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Diagnosis unknown	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Chronic endocarditis	6	Clear	4	1	0	1	0	0	2	0	3	0	80	20
Septicemia	1	Clear	0	0	0	1	0	0	1	0	1	0	0	100
Cystitis	1	Clear	0	0	0	1	0	0	1	0	1	0	0	100
Diabetes mellitus	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Broncho-pneumo.	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Duodenal ulcer	1	Clear	1	0	0	0	0	0	0	1	1	0	100	0
*Acute cholecystitis	2	Clear	0	0	1	1	0	0	2	0	2	0	0	100
Bartholin abscess	1	Clear	0	0	0	1	0	0	1	0	1	0	0	100
Acute fractures	4	Clear	4	0	0	0	0	0	0	1	0	1	100	0
Adenoma thyroid	1	Clear	0	1	0	0	0	0	1	0	1	0	0	100
Paranephric abscess	1	Clear	1	0	0	0	0	0	0	1	1	0	100	0
Kidney sarcoma	1	Clear	0	0	1	0	0	0	1	0	1	0	0	100
Infected leg	1	Clear	1	0	0	0	0	0	0	1	0	1	100	0
Empyema	2	Clear	1	0	1	0	0	0	0	1	0	1	50	50
Carcinoma, uterus	1	Clear	0	0	0	0	1	0	1	0	1	0	0	100
Osteomyelitis	2	Clear	0	0	0	2	0	0	0	1	0	1	0	100
Inguinal hernia	2	Clear	0	1	0	1	0	0	1	1	1	1	0	100
Varicose ulcers	1	Clear	0	0	0	1	0	0	1	0	1	0	0	100
Cholelithiasis	3	Clear	1	0	0	1	1	0	2	1	2	1	33	66
Bullet wound	1	Clear	0	0	1	0	0	0	1	0	1	0	0	100
Ischiorectal abscess	1	Clear	0	0	1	0	0	0	1	0	1	0	0	100
Appendicitis	11	Clear	7	2	0	2	0	0	3	8	3	8	84	16

Total number of cases	100
Number of negative cases	48
Number of positive cases	52

* This and the cases following are postoperative.

CODE TO PRECIPITIN REACTIONS: 0 = negative; ± = faint trace; ± = trace; + = light cloud; ++ = cloud; +++ = heavy cloud.
CODE TO CHEMICAL TESTS: + = positive; 0 = negative.

mixing the serum. A nitric acid protein test and an acetic acid protein test were done on each urine tested. The results of the precipitin test on the one hundred different urines is recorded on Chart I. A preservative was not added to the sensitized serum because of its tendency to cause slight cloudiness, thereby giving rise to possible source of error. Furthermore, all the urine specimens were collected at the time the sensitive rabbit serum was freshly prepared.

Fifty-two of the 100 urines examined gave a positive precipitin test. The chemical protein tests were positive in 40 cases. The results obtained by the chemical tests varied from the results of the precipitin tests.

Fifty-seven per cent of the surgical cases in this series presented a positive precipitin test. The large majority of these cases were postoperative. Of the medical cases in this series 49 per cent were positive. All precipitin tests were compared with clear urinary controls.

Conclusions. The following preliminary conclusions can be drawn from this study: 1. Blood protein was detected in 52 per cent of the cases studied. This blood protein can be specifically identified in the urines of the cases tested by the precipitin test.

2. The detection of specific blood protein in the urine by the precipitin test does not parallel the positive chemical protein tests.

3. The presence of blood protein in the urine is not characteristic of any particular disease or type of case.

4. The most marked reactions found in this series were in cases of tuberculosis of the kidney, pyelitis, pregnancy and cancer of the uterus.

5. We can account for at least some of the proteinurias with or without renal pathology, by the presence of blood protein in the urine.

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THE DIAGNOSIS OF TRACHEOBRONCHIAL TUBERCULOSIS.

By F. Maurice McPhedran, M.D.,
PHILADELPHIA.

(From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.)

The literature of tracheobronchial and "hilum" tuberculosis is voluminous. The major part of it deals with physical signs and symptoms assumed to be associated with this condition. The descriptions of the actual lesion as demonstrated by Roentgen ray are somewhat vague both as to site and appearance. Not a few observers report calcification due to tuberculosis in the majority of all patients, whether or not they have been exposed to an open lesion. Many are governed in their recognition of the pathologic and anatomic lesion by the presence of a tuberculin reaction, and the association of evidence such as underweight, fever, cough, night sweats, fatigue and dyspnea, which are generally assumed to be allied with and to result from the lesion. It is desirable to consider the possibility of consistent and reproducible demonstration of tracheobronchial tuberculosis. If we are to understand its pathogenesis and symptomatology, those cases showing roentgenographically reproducible lesions must be studied apart from the group whose anatomic diagnosis has rested on various symptoms. As has been shown elsewhere[1] these lesions are frequently the forerunners of diffuse pulmonary infiltrations. While there is no evidence that it is the source of these infiltrations, and much that it is not,[2] tuberculous tracheobronchial disease is an indication of severe infection, and such infection may not only be carried to the lymph nodes but may also remain latent in the lung and develop after the glandular disease gives evidence of healing.

The matter of roentgenographing the lungs and of determining what abnormal changes could be conclusively recognized has occupied the writer for some seven years. The subject was approached in two main studies, one to discover what elements of the lung structure might be differentiated roentgenographically under the simplest conditions, the other to provide against the effect of cardiovascular movement in disturbing lung detail. The mechanism, methods and some conclusions of the latter study[3] have already been briefly reported.

The former aim was sought by roentgenographing the excised lung, and then comparing the specimen, area by area, with the roentgenogram. Some 400 pairs of lungs were thus examined, about 150 of these being maintained inflated during exposure. Excised lungs have the advantage of relative availability and ease of handling; and slightly finer detail may be shown when the ray can

be decreased to what is just sufficient to penetrate the lung itself. Furthermore, no contiguous structures, such as spine, mediastinum and sternum, complicate the shadow, a matter of importance in discovering the roentgenographic demonstrability of normal and pathologic lymph nodes of the tracheobronchial and intrapulmonary groups. In this paper the lymph nodes lying within the lung will be described as intrapulmonary, those outside as tracheobronchial. The division is artificial pathologically but convenient for anatomic and roentgenologic descriptions.

In passing it may be noted that in this series of pathologic specimens, which was examined by Dr. Opie, the pulmonary primary lesion was demonstrated in the lung substance in all but about 1 per cent of the cases in which a glandular lesion was observed. It was at least as frequent that a pulmonary primary nodule occurred without a glandular lesion as that the reverse was found. Below are given the anatomic and roentgenographic characteristics by which particularly the lymphatic element of the associated primary pulmonary and glandular lesions[4] may be conclusively recognized. But the criteria apply equally to those pulmonary primary lesions which are situated in the parenchyma close to the main stems, for example on the medial aspect of the lung, subpleurally at the inner part of the interlobar fissures, or, more rarely, in the lung substance which lies about the main stems. Frequently the pulmonary primary lesion is larger than the glandular (Fig. 9), and constitutes a greater menace; frequently it progresses into a diffuse or localized infiltration, usually nonapical because the originating primary foci, distributed in proportion to lung volume, occur more commonly in the lower part of the pulmonary cone. But from the diagnostic point of view, the pulmonary primary offers few difficulties in recognition because it is usually situated subpleurally[4] and therefore occurs chiefly at the periphery (Fig. 9). It is, in consequence, rarely to be confused with or obscured by trunk shadows, and is obvious, unless it lies behind the cardiac or diaphragmatic shadow. Here too it may be demonstrated, if calcium-bearing, by the proper quantity of Roentgen ray. And even when calcium-free, if it lies clear of other densities, the pulmonary lesion can be recorded at least as well as the vascular branches of supply in the area in which it is situated. Excised lung studies show the calcium-free pulmonary primary to be as dense, per unit of volume, as artery or vein and consequently, when synchronization permits the recording of fine vascular detail, any equally fine pathologic detail will be shown at least as well. Subpleural densities are remote from the effect of cardiovascular vibration, described later, and if anterior, are especially favorably situated for accurate representation.

The term tracheobronchial tuberculosis is preferable to hilum tuberculosis because, as pointed out by Opie, the former describes accurately the glandular element of the complex of primary infection.

The lesion rarely breaks through the gland capsule, and if it does the rupture is usually into a bronchus, artery or vein. Direct progression through the capsule into the areolar tissue of the hilum was seen only once in a series comprising over 400 specimens, including many fatal infantile cases. While infiltations occur involving the parenchyma near the main bronchial and vascular stems, in our studies, both of postmortem material and of living persons, it could be shown by careful examination that there was also an apical lesion, and the presumption is that, for the most part, localization near the root is merely one of the less common manifestations of bronchogenic extension. Furthermore, it was notable in the excised lung series that frequently, in the presence of a slight apical lesion, a more definite infiltration in the upper part of the lower lobe or the anterior lappet of the upper lobe gave the roentgenographic appearance sometimes described as hilum tuberculosis. Even in good stereoscopic films in the living it is not always possible to define the plane in which a lesion lies. Section will decide the question in the excised, and variations in the patient's position will solve it in the living.

The postmortem material for this study comprised many lungs free from gross lesions or even agonal edema. From these a good conception was obtained of the number of trunks that might be recorded. They are strikingly more prominent (Fig. 1[5]) and numerous than in the films of normal persons in life, and more bronchial bifurcations, the site of nodes, are rendered visible. On section of the lungs special attention was directed to the possibilities of roentgenographic localization of the lymph nodes, both the normal and those showing various stages of fibrous and inflammatory change. Meticulous study of the films was made in cases showing diverse types of nodes, from the dense, fibrous, coal-pigmented lymph node of the city dweller, and the succulent nodes of acute, nontuberculous bronchopneumonia, through the stages of fresh semifluid and old putty-like caseation, to the stony nodules and masses of dense calcification. In summary, it was found, as regards the nodes of the trachea and extrapulmonary bronchi, that only when calcium infiltration of a necrosed area was present was there any distinctive shadow. As regards lymph nodes within the lungs, it was found that the presence of calcium was the only roentgenologic indication of the presence and site of a lymph node, except for that segment of the noncalcified margin of such large calcium-bearing glands as projected laterally to the main stems and larger branchings of the air and blood-bearing trees and so contrasted with pulmonary parenchyma. Intrapulmonary nontuberculous glandular enlargement sufficient so to project was not seen, although there were many specimens showing large, succulent glands due to acute infections. Such glands did not throw shadows to be differentiated in the composite shadows of the main stems and their branches

which cross and surround the glands, and this study affords us no reason to suppose that they may be recorded in the living, or confused with tuberculous disease. While this finding is contrary to the inferences to be drawn from many articles, it is in harmony with the properties of the Roentgen ray, which is obstructed, per unit of volume, only in relation to atomic weights. Furthermore, although many roentgenograms were made during and immediately after acute, often serious, infections in children at all ages, in no case was there evidence of roentgenographic demonstrability of glands of the tracheobronchial group referable to the acute infection, that is, calcium-free.

Reference to Figs. 1 and 2 (see also Fig. 1[5]) will show how well adapted to the fullest representation of any normal or abnormal density was the material studied and the method of making the stereoroentgenograms. The trachea and bronchi with their sheathing tissues stand out clearly. Except for the surrounding areolar tissue and occasional tags of the great vessels, all that might obscure the lymph nodes was removed. The lungs were inflated until the air entered everywhere, then allowed slightly to subside so that the pleura should not be unnaturally tense. The total volume of air contained, and consequently the basis for securing contrast was similar to that existing *intra vitam*. The lungs were allowed to hang freely, and it was sought to keep them in a position as nearly normal as possible merely by their apposition to the front of the cassette changer. Occasionally string or gauze was used to separate the bases. Stereoscopic exposures were made, the duration varying from one-fiftieth second to one-twentieth second; rarely as much as one-tenth second was used. The photographic effect sought was that giving the greatest detail. The relation of the quantity of exposure to that of the living was about 60 to 75 per cent. The absence of the chest wall reduced the amount necessary. It was found that full exposure, as for the living, marred the detail in the periphery but that otherwise the films were similar.

Clearly, tracheobronchial lymph nodes, both those lying immediately outside the lung and those further cephalad on the bronchi and trachea, are favorably situated, in the excised lung, for the fullest demonstration of changes in contour and density. Yet in all the specimens studied partial outlines of only two lymph nodes could be made out lying within the shadow cast by the ensheathing areolar tissue. In all other cases, apart from calcium infiltration, when the site of nodes could be determined from the film, it was due to enlargement; whether the cause of the enlargement was coal-pigmented fibrous tissue or acute edematous swelling, its indication of the site was due to the size, not to the intrinsic density of the node. That is, only in instances where the node projected laterally from the trachea or bronchi, bulging out the sheath of areolar tissue, was its contour indicated. Otherwise, even if a

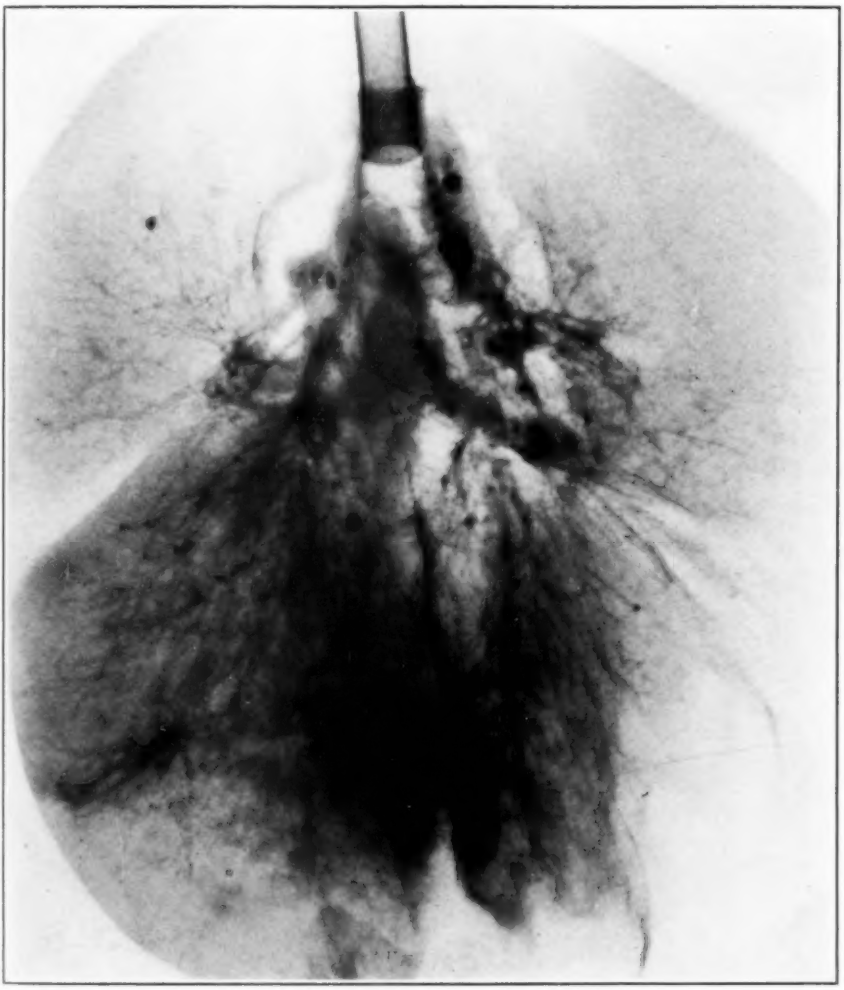

FIG. 1.—Right lung: The vessels were not tied before section. Inflation expels most of the unclotted blood and these lungs contain little. Neither the arterial nor the venous main stem can be seen. On section, the upper and middle lobes are dry, the lower red and contains fairly abundant fluid. At the hilum, the carina and to the right of the trachea are hard, anthracotic, fibrous lymph nodes containing hard calcified masses. Left lung: The left lung resembles the right. There is a firmly calcified nodule in the upper lobe. The nodes at the hilum resemble those on the right. There is no evidence of the presence of the uncalcified part of nodes except for the calcium-containing bulge above the left bronchus. The fibrous, pigmented glandular margin is no denser than the ensheathing areolar tissue.

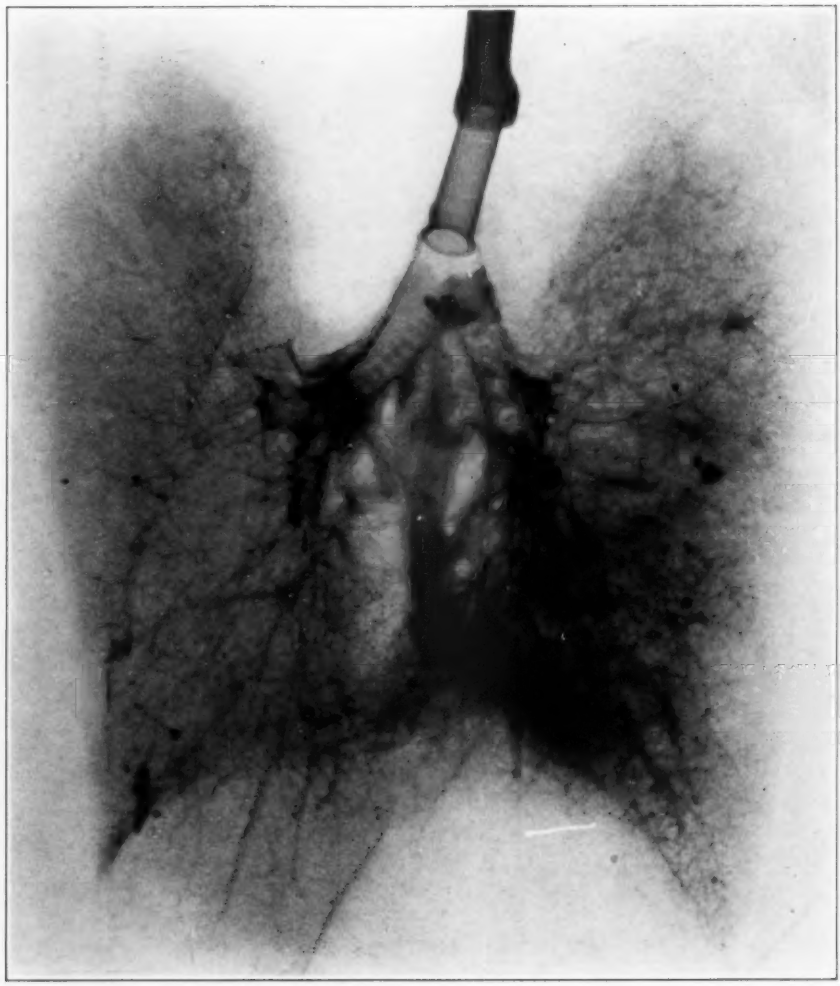

FIG. 2.—The vessels were not tied before removal of the lungs. There is a dense calcium shadow at the carina, two others lateral to the right main stem bronchus and one in the substance of the right lung. The glands containing the calcium at the carina and on the bronchus are not distinguishable, although the one at the carina is particularly favorably situated. The fibrous capsule enclosing the mass in the lung substance throws a faint halo-like shadow.

FIG. 4.—A postero-anterior view. In the right tenth interspace, *G*, is a rounded density, due to a vessel directed toward the target, that is axial to the incident ray. Similiar densities, *H* and *I*, appear on the arterial main stem shadow. On the left seventh rib is a dense, irregular, club-shaped shadow, *A B*, 1.7 x 0.7 cm., its head touching the aortic contour. One centimeter lateral to its lower end is another dense shadow, *C D*, 1.3 x 0.6 cm. In front of the eighth rib, on the arterial main stem shadow, is a granular density, *E F*, 1.7 x 0.8 cm..

FIG. 5.—*A B, C D, E F,* and *G* are still seen in this exposure made at the lower stereoscopic level. *H* and *I* are not clearly recognizable. *E F* is better seen below the eighth rib shadow, than in the former figure, in which it lies in front of the rib.

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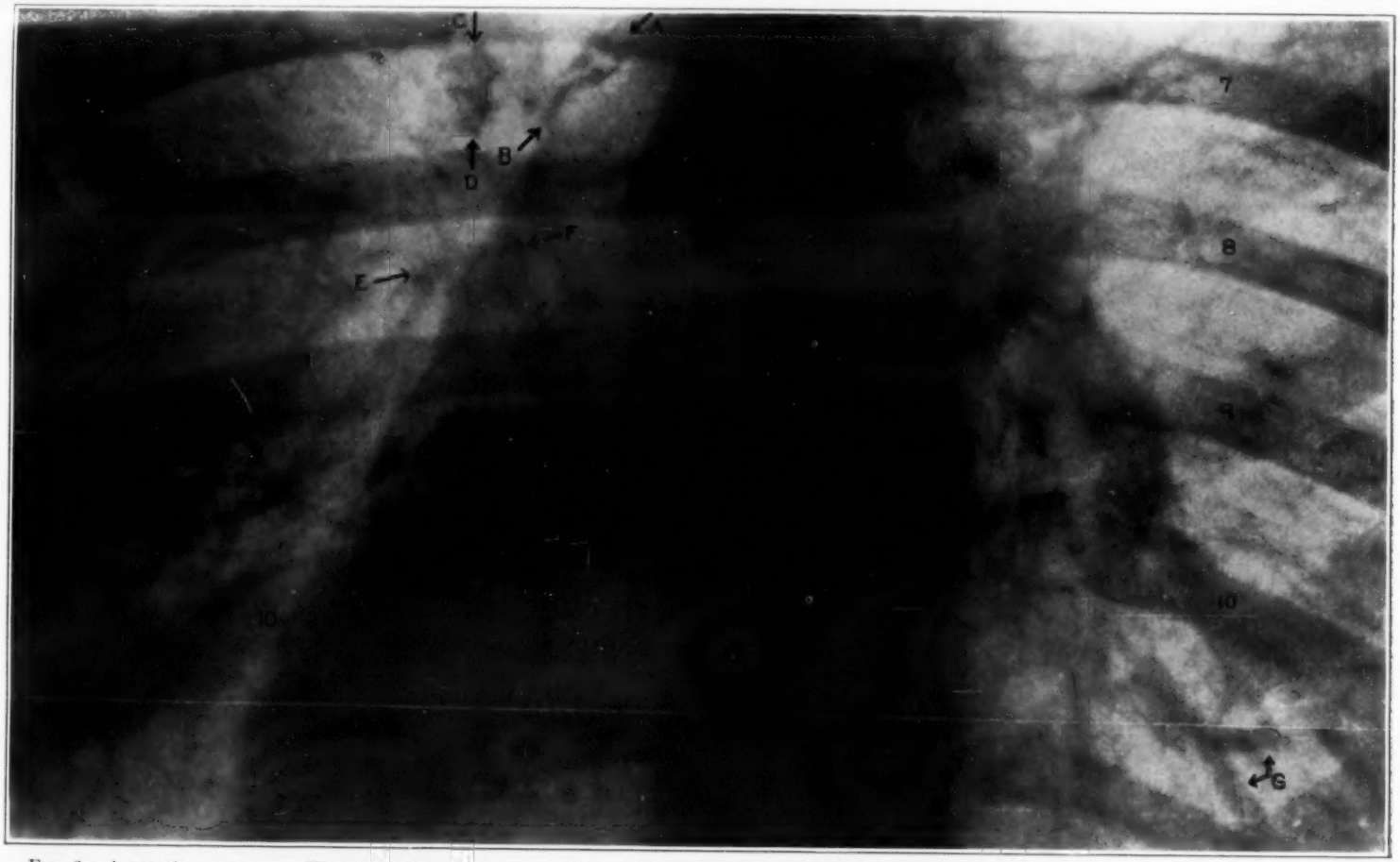

FIG. 6.—A rotation exposure. The rounded spot *G*, in the right tenth interspace is replaced by a Y-shape vessel, the upper arm of which, axially radiated, caused the density *G*. The lesions on the left can be recognized as persisting. *C D* is more clearly defined, seen from the new angle; *E F* in the eighth interspace is now partly behind or upon the cardiac shadow.

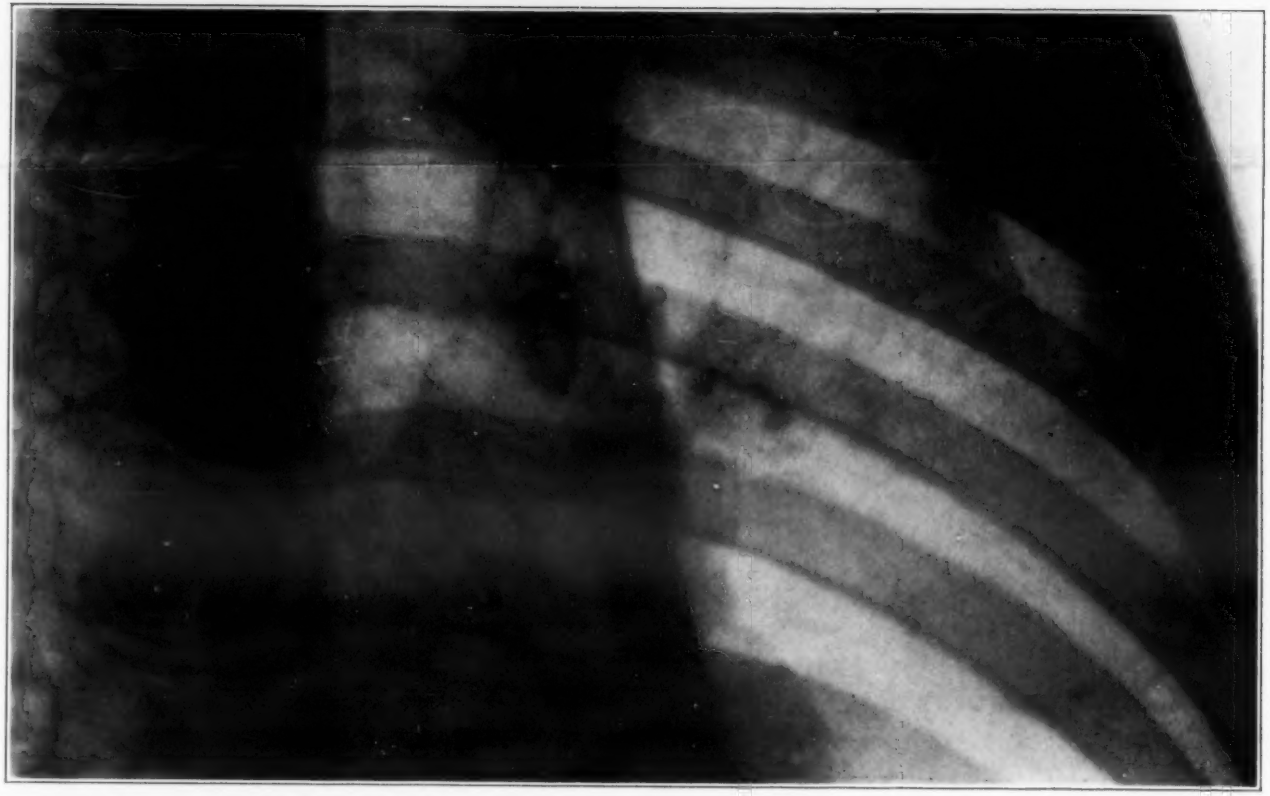

FIG. 7.—This patient's father had positive sputum in February, 1924, and was at home almost continuously until his death, in February, 1926. In this oblique view a granular shadow, 2.2 x 1 cm., can be seen just to the right of the carina. This is due to a relatively light calcium infiltration in a large necrosis. There was no mediastinal bulge.

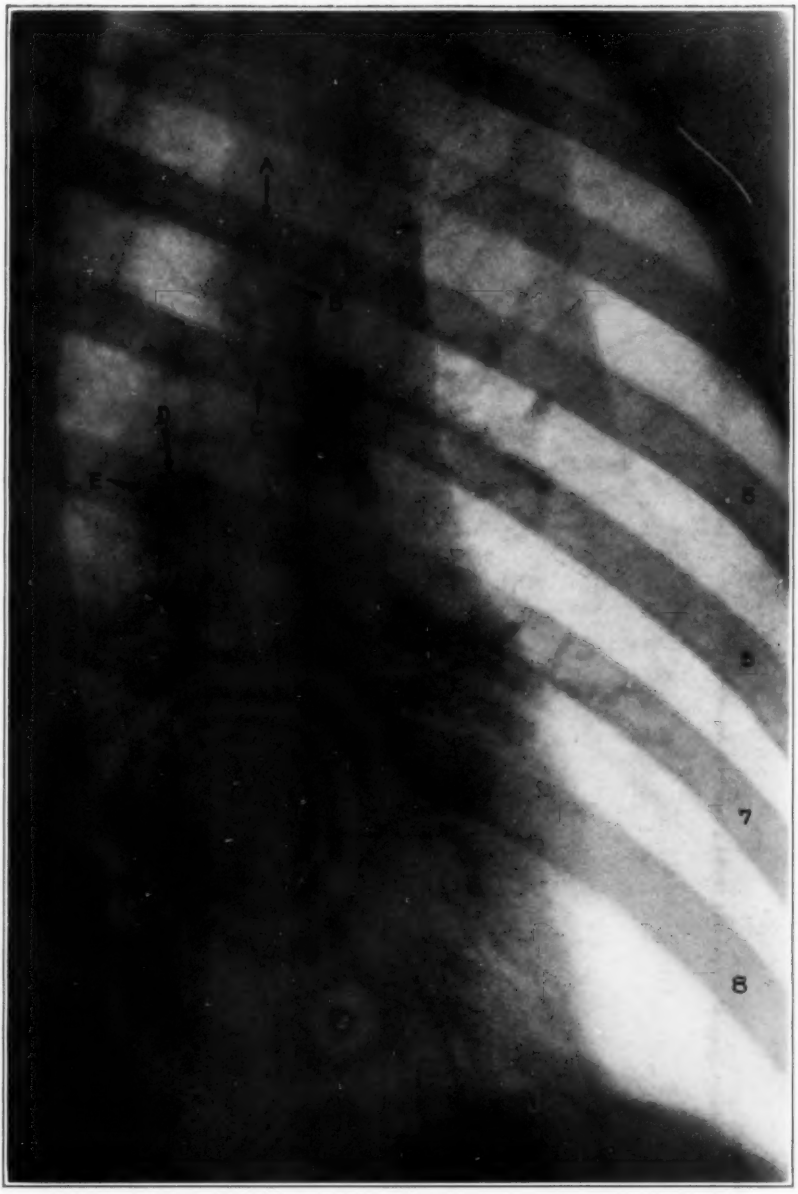

FIG. 8.—Left anterior oblique exposure of a boy, aged seven and a half years, in contact with a tuberculous father (sputum positive) during four and a half years until one and a half years prior to this roentgenogram. Close to the right side of the trachea, above the carina, at the level of the fifth rib and interspace and the sixth rib are two oval outlines. The lower pole of the upper one, the long axis of which is indicated by *A*, overlaps the upper pole of the lower one, the long axis of which is indicated by *C*. Their lateral borders cross at *B*. The lower one is not unlike the nucleus of an epithelial cell, with a dark, oval outline and an irregular dark spot within it, at the sixth interspace level. *D*, *E*, *F*, mark the upper pole, posteromedial border, and lower pole of another oval density lying posteromedial to the right bronchus below the carina, which is crossed by the sixth rib. These densities are due to scant calcium infiltration of caseous glandular necrosis. Neither of these shadows could be seen in the postero-anterior position. The outlines of the glands enclosing the calcium-bearing necrosis can be seen neither in the illustration nor in the film from which it was taken. There was no mediastinal bulge. The left bronchus passes in front of the spine at the level of the seventh rib. The lower end of the right bronchial main stem is marked by *G*. The patient was well nourished and active, pulse and temperature were normal. There were no complaints nor symptoms.

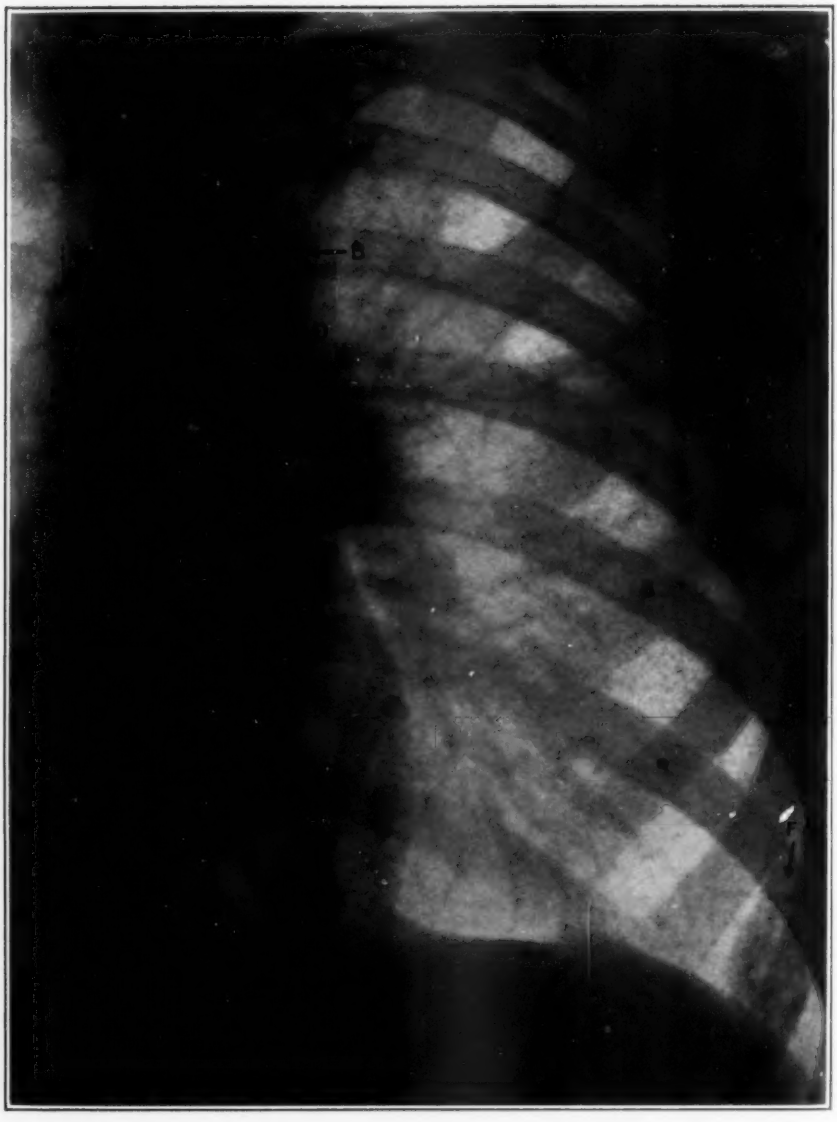

FIG. 9.—Patient, aged five years. Exposed to open lesion of mother for about three years. Child is apparently well. The patient is almost in an oblique position in order to throw the mediastinal lesion clear of the spine. The head of the left clavicle is behind the spine; that of the right lies lateral to the spinal right border. In front of the ninth rib and interspace and the tenth rib is a pulmonary lesion *F G*, 2.6 x 1.3 cm., lightly infiltrated with calcium. On the arterial shadow in the seventh interspace is a calcium shadow, *D E*, 1 x0. 8 cm. Lying on the right tracheal wall in front of the fifth interspace, sixth rib and interspace and seventh rib is a similar shadow *A B C*, 2.3 x 1.3 cm. The trunk markings reproduce faintly but a uniform and regular radial striation may be seen. There is no shadow of diffuse pulmonary infiltration.

node contained calcifications or caseation impregnated with calcium, the shadow recorded conformed only to the outlines of the calcium-bearing lesion. The peripheral lymph tissue, whether hypertrophic or fibrous, and the gland capsule were not dense enough to cast a shadow differentiating them from the contiguous areolar tissue. Glands containing soft fresh caseation due to acute, rapidly advancing infections were similar in density to nonspecific edematous nodes. They were distinguishable only if large enough to bulge out the silhouette of the areolar mantle (Fig. 1.)

In discussing the recognition of intrapulmonary lesions, it is necessary to consider at each point what modifications of the appearances seen in roentgenograms of the excised lung are effected by cardiovascular movement in films of the living. The intrapulmonary nodes and lymphoid masses, situated at the forks of branchings of the bronchial tree, are surrounded by structures of roentgenographically equal density. In proportion as one approaches the hilum and the nodes are larger, they are crossed, surrounded and overlaid by arteries, veins and other bronchi converging on the main stems. The vascular trunks, at least, are, per unit of volume, as dense to the Roentgen ray as are normal nodes, or, indeed, any nodes, without calcium infiltration, as pointed out above. The glands most frequently and severely infected, those which lie just lateral to the main stem bronchus (Figs. 1, 2 and 4), that is, on the side whence the bronchial trunks arise, are not only crossed by the venous trunks but have superimposed on them the main arterial stem. In order for nodes so situated to be recognizable roentgenologically they must, unless containing calcium, project not only beyond the shadow of the main arterial stem but also beyond the zone where the crossing of the converging vascular trunks forms a complex, unequal shadow, for only so can they be shown in contrast to the air-bearing parenchyma. In the living this zone is particularly confusing when the exposure is as long as the cardiac cycle, because of the effects of cardiovascular movement; or, when a shorter time is used, if the exposure chances to occur during systolic movement. Diastolic rapid exposures (not more than 0.05 second at pulse rates about 100), are best adapted to show the origin, course and branchings of trunks, and to differentiate abnormal glandular enlargements which may project into this zone.

We have seen, in our excised lung series, no instance of a noncalcium-bearing gland projecting beyond the arterial main stem shadow, and only one instance in the living. In this case repeated, but not yet protracted, observations, suggest a tuberculous etiology. Not infrequently a calcium-bearing gland is seen to project, and to show, laterally, a margin surrounding the calcium-bearing necrosis, its peripheral contour standing out against the less dense pulmonary parenchyma into which it bulges. It is somewhat more common to find such a gland to lie wholly medial to the lateral margin of the

arterial main stem. Then only the calcified area is visible (Figs. 4, 5 and 6), the remainder of the gland being no denser than the arterial main stem shadow and the maze of vascular trunks abutting on it and crossing it in many directions.

A common source of diagnostic error is the sharp, round shadow cast by a vascular trunk directed toward the target so that the incident or primary ray is approximately axial (Figs. 3, 4, 5 and 6); or the semioval shadow often recorded when the plane of the curve of a vascular trunk is directed slightly above or below the axis of the ray. Each of these is comparable to and often situated beside the dense ring-shadow due to a bronchus directed toward the target. The former is more common and may occur anywhere in

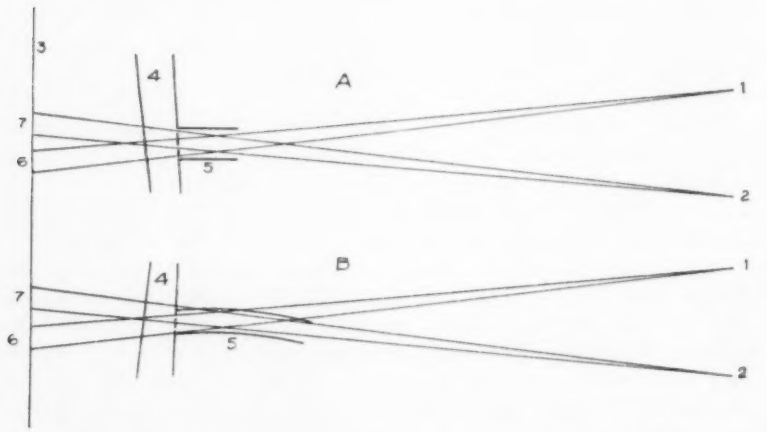

FIG. 3.—The stereoscopic drop is exaggerated to facilitate drawing. Actually the two rays intersect at a more acute angle and may consequently be practically axial to narrower vessels. 1, Ray from upper position of tube; 2, ray from lower position of tube; 3, stereoscopic films, represented as one; 4, vessel directed in plane perpendicular to axial rays; 5, axial branch; 6, shadow cast on film 1; 7, shadow cast on film 2.

the lung field except at the apex and the extreme lateral margin, inasmuch as branching of trunks continues well out to the periphery. In proportion as caliber diminishes these shadows of vascular causation are smaller peripherally. Those trunk shadows radiating from the hilum in planes nearly perpendicular to the incident ray often show the branches which arise from them axial to the ray as more or less well-defined dots particularly in the middle and outer third of the lung field (Fig 1[5]). Many of these dots are ill-defined and blurred when exposures occur during systolic movement and have been interpreted as thickening of the trunk on which they appear. The apical branches of supply, however, running straight into a rapidly narrowing cone, are little disturbed by vascular movement and frequently show these dotted vessels.[6] Thus

branches arising parallel to the axial ray are responsible for many "beaded" trunks and practically always for the so-called "capped" trunks, which have been interpreted as due to calcium in a lymphoid mass at the bronchial bifurcation. In films of the excised lung, when the vessels are tied off before removal, the number of these round and oval shadows along the course of the vascular trees is amazing, and their nature may be verified by section. Practically, both for the excised and the living, the diagnosis may be made conclusive by appropriate methods. The proof lies in roentgenographing the beaded trunk from a slightly different angle, when it is seen that the dots have disappeared and that branches arise from their site. On the other hand, a calcified lymph node or pulmonary nodule may show a variation in contour but will not be lost by this procedure (Figs. 4, 5 and 6). For many such determinations the distance of the stereoscopic shift supplies the necessary new angle of radiation, when the films are truly stereoscopic, that is, when the lungs are undisturbed by changes in relative cardiac volumes and by differences in pressure in the elastic vascular tree.[6] In other instances the conclusive differentiation of vascular artefacts from calcium-bearing lesions by stereoscopic exposure alone is not possible. It is apparent that even with a full stereoscopic drop and rapid diastolic exposures, the incident ray from both the target levels will be practically axial to the shorter, thicker trunks that run parallel to it (Fig. 3), or even to those narrower trunks whose natural curve forms an arc to the axial rays, so that at both stereoscopic levels a dense column of blood is opposed to the ray. The former condition frequently obtains upon and close to the arterial main stem, and medial to the main stem bronchus, due, respectively, to arterial and venous axially directed branches. Such vascular artefacts are especially disturbing in films of infants, and troublesome in those of older children. In infants the trunks closest to the main stem cause the artefacts, and these are large enough in proportion to the chest to suggest serious lesions. The older children show more numerous artefacts, since there are more vessels large enough to throw a shadow. Often in children of ten to fifteen years the very number and the uniformity of size, quality and distribution of these shadows is enough to cast doubt on their having a pathologic significance.

The type of vascular artefacts due to a curving vessel axial to the incident ray is seen commonly at the posterior level of the fifth and sixth interspace, right and left.

It was found that exposures made at various points above and below the usual stereoscopic upper and lower levels commonly failed to solve the nature of those questionable shadows. This is due to the large number of branches arising at every level from the main vascular stems. Thus one could not be sure, even after a shift, of, say, 7 inches below the usual stereoscopic midpoint, if a

persisting density were not simply a new vessel coming off lower down. It was then found that a slight rotation of the patient about his perpendicular axis was of great value in deciding the question. After many trials, I have sought to rotate the patient so that the right cardiac border coincides in the film with the right border of the spine. A single exposure so made at the lower stereoscopic level has enabled us to determine the identity of practically all densities lateral to the spinal border, right and left (Figs. 4, 5 and 6). Only very occasionally is it desirable, chiefly for the diagnosis of densities lying near the bronchus to the left upper lobe, to rotate the patient in the opposite direction (that is, the right shoulder and hip away from the cassette changer, and to the same degree as for the above noted left-shoulder-off position).

The addition to the usual stereoscopic technique of the first described left rotation (left side away from the film) is of value not infrequently in the diagnosis of lesions sufficiently unstable to warrant careful oversight and reduced exertion to ensure their healing. Many intrapulmonary unencapsulated caseous necroses, containing only delicate and diffuse calcium infiltrations, can be certainly diagnosed by the addition of slightly rotated exposures. A true lesion will continue to be recorded in the rotation film as a shadow of constant quality, finely and irregularly granular, or made up of softly lamellated and crenated lines (Figs. 4, 5 and 6), or irregularly stippled; and its contour will show such slight changes as will be harmonious with that in the postero-anterior position. Artefacts, on the other hand, are resolved into their components or entirely disappear. Especially valuable is the rotated position in differentiating from true lesions the very common densities in the right cardiophrenic angle due to venous trunks, and the numerous spots in the inner third of the lung field due to arterial and venous branches. It is also often useful when it is of moment to diagnose densities in the outer half of the lung field. Naturally, as the caliber of the vessels diminishes peripherally, lesions likely to be confused with densities of vascular origin are smaller and of less clinical importance. Care must be taken not to turn this exposure into an oblique (see below), for in the oblique position a new and, for this purpose, confusing number of rounded densities occur, and it is difficult to determine which shadows one was seeking to resolve.

In many cases a position midway between the postero-anterior and the lateral is indispensable. In the roentgenographic recognition of tracheobronchial tuberculosis in the living, the shadows of spine and sternum offer a serious difficulty. Without the oblique exposure it is impossible to recognize clearly (see Figs. 7, 8 and 9) or even to suspect the presence of fresh and unstable tuberculous necrosis. Many calcium-bearing lesions, both at the carina and to the right of the trachea, measuring up to 2.5 cm. across, completely escaped demonstration in the postero-anterior position

(see Fig. 8, *D, E, F*). It is perhaps important here to emphasize what has been said above with reference to the excised lung, that calcium-free caseation, apart from mass and consequent projection into the lung field, is roentgenologically indistinguishable from the areolar tissue and vessels of the mediastinum. Caseation so extensive as to bulge into the lung field, a condition chiefly seen in infancy, must almost invariably prove fatal. In the living it is rare that a calcium-bearing tracheobronchial gland can be seen to project beyond the margin of the spinal shadow. We have not seen tuberculosis of the tracheobronchial glands cause a uniform, rounded mediastinal mass except in fatal infantile cases. A postero-anterior film showing smooth and oval mediastinal bulges should be scrutinized for distortion of the patient's position by which the shadow of the sternum appears to the right or left of the spinal shadow. Malignant tumors will rarely come in question in children. Rotation is probably responsible for the majority of apparent mediastinal enlargements. It is in infants and in children up to four years that most "broadened mediastinums" have been interpreted as pathological. Apart from errors due to rotation and to thymus shadow, exposures made during systole and during expiration are frequent causes of broadening of the mediastinum. After the fourth year response to the request for holding the breath is obtainable, and broadened mediastinum is rarer.

The chief value of the oblique position is that one is able to record the trachea, the carina and the two bronchi as far as their entrance into the lung in a way that is not possible when they are situated between the spine and sternum. Calcium-bearing necrosis throws its characteristic shadow, and while the gland in which it lies is not to be outlined, from the nature of the granulation, whether faint and small, or large, dense and confluent, one can estimate the condition and lability of the lesion. The longer calcium infiltration has endured, the better are the chances that the lesion has been walled off. We have, in three years observation, of cases reported elsewhere[1] found no evidence of reabsorption of calcium from glandular lesions. In several cases the shadow has become heavier and better delineated. Insofar as the glands are concerned, caseation if accompanied by calcium infiltration, appears to remain. In view of clinical and experimental evidence[8] that reabsorption of caseous pulmonary and glandular infiltration occurs further and more extended observations on calcified glandular caseation are desirable.

The situation, extent and contour of the calcium-bearing glandular lesions have been of interest. As pointed out by Opie[4], the common lesion in a lymph node above the carina (Figs. 1, 7 and 8) is almost always situated to the right of the trachea irrespective of the side in which the pulmonary and intrapulmonary glandular lesions occur. In the oblique view, it may be seen that the calcium-

bearing lesions lie close to the trachea and bronchi, and always, in our cases other than fatal infantile disease, leave a clear space between the posterior margin of the calcium-bearing mass and the spine.

The contour of the calcium shadow is various; rounded, oval, irregularly nodular, pear-shaped. But in all instances verifiable from two angles, a contour, however hazy, is perceptible. The contour may, of course, be referable to lesions in one gland or in more than one in apposition (Fig. 7, to right of trachea), in a plane lying parallel to or at various angles to the incident ray. Occasionally it is desirable to make oblique exposures at various angles to see the full extent of large lesions situated one behind the other in the line of the incident ray.

The oblique position used is one very similar to the left anterior oblique of Pritchard.[8] A good view of the trachea and bronchi is obtained by using a position almost half way between the postero-anterior and the lateral. In the more nearly lateral positions there tends to be superposition of the two hilum shadows and the carina is not seen. In the oblique position the shadow of the aorta lies behind that of the spine. The trachea, carina and the full extent of the extrapulmonary bronchi are well seen. The patient stands with the head slightly inclined, the left arm hanging behind the left hip, the left antero-lateral chest wall against the cassette changer, the right forearm bent over the head, the elbow as high as possible. The scapula thus interferes not at all with the view of the carina and right bronchus. Films taken in this position show many rounded and oval densities due to trunks axial to the incident ray. These are usually not confusing in the lower third over the heart shadow, but may be so just to the right of the right bronchus where it leaves the carina. These densities, however, rarely have the granular or stippled quality of calcium infiltration, and they change in quality and contour on slight rotation of the right side forward or backward. If these shadows due to vessels running to the apex prove confusing, the oblique exposures may be made with the right side closer to the cassette changer. The trunks then appear as curving or snarled ascending linear shadows.

Physical Signs. Our experience with physical signs in the diagnosis of tracheobronchial disease has been disappointing. Prolongation of the distinct whispered voice downward was common to the third, and not infrequent to the fifth dorsal spine; but we were unable to account for it on the basis suggested by d'Espine. The level to which it was heard often varied in the same individual depending on whether the head were erect or slightly over-extended, or bent forward, being lowest in the last position. Possibly this is due to some increased conductivity of the tissue between the trachea and the spine. But there was in our cases no definite relation of the sign with the presence of calcium-bearing tracheo-

bronchial glands, and, as noted above, none such could be seen extending to the spine (see Figs. 7 and 8.)

Percussion gave almost equally unsatisfactory results. There was no constant relation between apparent changes of percussion note and a demonstrable lesion.[9] It is not easy to understand how lesions other than the massive caseation of fatal infantile tuberculosis, which alone, apart from the malignant tumors, protrudes materially beyond the spinal margin, could supply an anatomic basis for changes in percussion. The width of the mediastinal shadow must be considered in relation to type of chest, fat, depth of respiration and cardiac phase. A mediastinal shadow extending uniformly 1 cm. beyond the spinal margin for the length of two posterior interspaces has been seen in the short, thick-set build at about the fifteenth year. We have seen esssentially this same mediastinal outline both in normal noncontact children without a lesion and in a child with a calcium-bearing lesion 3 by 3.2 cm. lying behind the trachea and lapping for 1.4 cm. beyond the right tracheal wall. This child had been exposed to a source of infection for one year three years previously.

Nor is there commonly a well-defined basis for those changes in percussion in the interscapular region ascribed to changes in muscle tone. If such changes occur and be referred to reflex effects, one must usually assume that caseation within a gland is the cause. For while caseation involving the gland capsule and spreading to the tracheal wall is not uncommon enough to be a postmortem rarity, neither is it so frequent as to be invoked as explanation in the average clinical case.

Symptoms. We have not as yet been able to recognize a characteristic or definite group of symptoms due to tracheobronchial tuberculosis. For example, the child whose film is shown in Fig. 8 looked well and gave no complaints. Malnutrition and fatigue occur perhaps more often in affected children than in others in the same environmental and sociologic status. Respiratory symptoms have been lacking in cases of uncomplicated tracheobronchial disease. It is essential to rule out parenchymatous infiltration when cough or dyspnea is present. This requires, especially in young children very careful technique. Neither in postmortem material nor in the living have we seen evidence that tuberculous tracheobronchial enlargement may give rise to mechanical stenosis. The areolar tissue about the tracheobronchial nodes and the parenchyma of the lung are very much more easily displaced than the air-passages. Unquestionably, extension of caseation through the gland capsule, if it involves the tracheal or bronchial wall, will cause respiratory symptoms. But in these cases it is reasonable to assign them to the concomitant inflammation. Even evidence of stenosis of branches of the vascular tree has been lacking. When this diagnosis is suggested from the prominence of trunk markings

arising near a calcium-bearing gland, it is well to look closely for infiltration in the lung supplied by the prominent branches. Decreased pulmonary elasticity, with consequent reduction of vibration set up by the pulse wave, is much more frequently a cause of locally prominent trunk markings than is thickening of the trunks, whether by disease of the wall or by increase of content. This, however, is a subject to be dealt with more fully elsewhere.[10]

Tuberculin Reaction. The quantitative tuberculin reaction is important at those ages at which it is most desirable to recognize the presence, pathologic condition and significance of tracheobronchial tuberculosis. A full statement of the value of the test is given elsewhere[1] but certain of its correlations which are pertinent in the consideration of tracheobronchial tuberculosis are cited here.

It has been found that, in the urban population studied, marked reactions with the lowest quantity used, 0.01 mg. O. T., are the rule at maturity, but that the younger the child the more often is such susceptibility a result of intimate contact with an open pulmonary tuberculosis. And of those children having the more severe reactions, almost two-thirds showed roentgenologic evidence of the primary complex, in large part lesions involving the glands. From the other point of view, considering the group with demonstrable tracheobronchial lesions, 90 per cent reacted with 0.01 mg. of tuberculin. These facts must be aligned with the evidence cited above, that only the presence of calcium infiltration allowed one to perceive the presence of glandular lesions, and with the observed interval of over three years that usually elapsed between the onset of intimate exposure to a source of tubercle bacilli and demonstrable calcium infiltration of the glands. (Calcium commonly appears earlier in a parenchymal lesion.) Therefore, in infants a tuberculin reaction, especially if intense, is in itself an indication for the institution of every measure calculated to improve the child's condition, and above all to prevent the lodgment of additional bacilli, whether a lesion can be shown or not. As stated above, tuberculous glandular enlargement sufficient to bulge beyond the spine shadow in infants is, in our experience, of fatal import. A working diagnosis and an urgent therapeutic indication is established by the tuberculin reaction alone at this age. A marked reaction to 0.01 mg. of tuberculin in a child under five years is still sufficient to warrant therapeutic and preventive means even in the absence of demonstrable lesion. The presence of a recognizable lesion gravely emphasizes the danger and rarely before the fifth year will the calcium shadow be other than fine and presumably labile (Fig. 9). After the fifth year an intense reaction suggests an active lesion especially if the calcium infiltration casts a soft shadow.

The diagnosis in the individual of tuberculous tracheobronchial disease must rest on a demonstrable lesion, and a definite symptom complex can be discovered only by study of cases presenting such

lesions. If diagnosis is to constitute a basis for adequate treatment, it is essential to seek out the infecting source. Intense tuberculin reactions in several children of the same household may point to an unsuspected or to an apparently arrested source of infection. The prevention of massive or prolonged reinfection is no less essential to the rational treatment of the tuberculosis of childhood than to any radical prophylaxis deserving the name. Comparisons of the incidence and intensity of tuberculin reactions and demonstrable lesions in contact and in noncontact families, point to the paramount influence of contagion on the development of tuberculous disease in children. There is reason to believe that from the latent infections of individuals heavily infected in childhood develops the manifest tuberculosis of young adult life, economically the most wasteful form of the disease and, in its turn, the prolific source of latent disease in others.

Conclusions. 1. Study of postmortem material shows that calcium infiltration is the sole distinctive roentgenographic indication of the site of a lymph node situated within the limits of the mediastinum. Calcium-free glands, however enlarged, fail to cause perceptible intensification of the mediastinal shadow.

2. The protrusion of the mediastinal wall beyond the shadow of the spine and sternum by caseous lymph nodes is rare except in fatal infantile cases.

3. Intrapulmonary glands must contain calcium to be recorded roentgenographically. When they are large, that part of their calcium-free margins which projects beyond the arterial main stem will be recorded by contrast with the pulmonary parenchyma.

4. It appears that reabsorption of calcified caseous necrosis within lymph nodes does not occur.

5. Shadows simulating calcification are thrown by vessels axially radiated.

6. No symptom complex has been found characteristic of tracheobronchial tuberculosis. Respiratory symptoms due to uncomplicated tracheobronchial disease do not occur.

7. The quantitative tuberculin reaction gives important indications as to the activity of the lesion in the individual. It is of unique value in infancy. It gives indispensable information regarding the source of infection, ignorance of which frustrates alike treatment and prophylaxis of tuberculous disease at its most tractable phase.

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CHRONIC INFECTIOUS ARTHRITIS.

An Analysis of 200 Cases

By Russell L. Cecil, M.D.,

and

Benjamin H. Archer, M.D.,

new york city.

(From the Cornell Pay Clinic and the Second (Cornell) Medical Division of Bellevue Hospital.)

The object of this study has been to define more clearly the clinical features of chronic infectious arthritis as distinguished from other forms of arthritis and to evaluate the various measures which have been employed in its treatment. This investigation is based on 200 consecutive cases of infectious arthritis which have come under our observation during the past four years at the Cornell Clinic. In a recent study by the writers[1] of 612 cases of chronic arthritis, 379 fell in the infectious group. The first 200 of the latter form the material for the present study.

In a previous communication[2] we have described a form of chronic arthritis which is not uncommonly seen in association with the menopause. In that study the conclusion was reached that arthritis of the menopause is probably noninfectious. If certain forms of chronic arthritis are not of infectious origin, it is very important to learn to differentiate them from the infectious type. The theory of focal infection has been so widely accepted that many clinicians now consider all arthritis an infectious disease. As a matter of fact chronic infectious arthritis is a definite clinical entity which can usually be distinguished from other forms of joint disease. Under the term, chronic infectious arthritis, we have included those cases which presented the picture of a chronic proliferative arthritis of distinctly inflammatory character, almost always migratory, and usually associated with one or more foci of infection. Cases

of specific infectious arthritis (gonococcus, tuberculous, staphylococcus, and so forth) have not been included.

Incidence. Chronic infectious arthritis has been by far the most common type of arthritis seen at the Clinic. Of all the cases of chronic arthritis admitted to the Clinic, 62 per cent have been of the infectious type.

Sex. There were 119 females and 81 males. This is in accordance with the findings of other observers who have noted the preponderance of chronic infectious arthritis in the female.

Age. The average age at onset for male patients was 34.5, for females 35.6. The youngest patient was four years of age and the oldest was sixty-one. The incidence of the disease according to decades is shown in the following table:

TABLE I.

Age at onset.	No. of cases.
1 to 10	3
11 to 20	14
21 to 30	62
31 to 40	57
41 to 50	43
51 to 60	21

It will be seen from this table that infectious arthritis begins most frequently in the third and fourth decades. This is in sharp contrast to the age incidence of arthritis of the menopause which occurs nearly always in the fifth or sixth decade.

Races. Practically all races were represented. There was no evidence of any racial predisposition.

Occupation. Most of the women were housewives. Of the 55 males who stated their occupation 33 were engaged in indoor and 22 in outdoor work. Infectious arthritis is apparently just as common in those who are sheltered as in those who are exposed.

Weight. The average weight of the males was 150.5 pounds, of the females 140.1 pounds. The age, height, weight relationship was determined for 59 females. The average age was 34.8, the average height was 5 feet 3 inches, the average weight was 139.9 pounds, as compared with the normal weight of 132 pounds for women of this age and height. The same relationship was determined for 41 males. The average age was 36.9, the average height was 5 feet 7 inches, the average weight was 146.8 pounds, as compared with the normal weight of 151 pounds for men of this age and height. These figures are quite different from those determined for menopause arthritis in which the patients averaged 43 pounds overweight. Generally speaking, individuals afflicted with infectious arthritis do not display such robust good health as those with menopause arthritis.

Etiology. All recent investigators of chronic infectious arthritis are agreed that the disease originates from some primary focus of

infection. Our investigations have led us to the same conclusion. The following table indicates the location of the various foci of infection that were demonstrated:

TABLE II.—LOCATION OF FOCI OF INFECTION.

Tonsils	68	Teeth and cervix	2
Tonsils and teeth	30	Teeth and middle ear	1
Tonsils, teeth, and cervix	6	Colon	7
Tonsils and cervix	5	Prostate	5
Tonsils and prostate	5	Pharynx	4
Tonsils and gall bladder	2	Cervix	4
Tonsils and colon	2	Sinuses	4
Tonsils and sinuses	2	Middle ear	1
Tonsils and osteomyelitis	1	Gall bladder	1
Tonsils, teeth and prostate	1	Pharynx and pyelitis	1
Teeth	21	Cervix, appendix and tubes	1
Teeth and prostate	2	Pharynx and colon	1
Teeth and pharynx	2	Gall bladder and pharynx	1
Teeth and gall bladder	2	None found	18

Infected tonsils were the commonest focus of infection, occurring *either alone or in combination with other foci* in 61 per cent of the cases. Next in frequency were infections about the teeth. Only those teeth were considered as foci of infection which showed severe pyorrhea or apical abscesses by the Roentgen ray. The teeth *alone or in combination with other foci* were the seat of infection in 33 per cent of the cases.

The sinuses were diseased either alone or in combination with the tonsils in 6 cases. The prostate was considered the source of infection either alone or in association with other foci in 13 cases. We were particularly interested in the relationship of gall bladder disease to chronic arthritis. The gall bladder was infected either alone or in association with other foci in 6 cases. Infectious arthritis is probably referable to the gall bladder more frequently than is generally supposed. One of the authors has recently seen 2 other cases of infectious arthritis in which the focus of infection was undoubtedly in the gall bladder. A good many of the cases of infectious arthritis occurring in middle-aged women without demonstrable foci are probably referable to infected gall bladders. Colitis, either of the mucous or ulcerative type, was present in 10 cases. Judging from our own experience the intestine has been overstressed as a focus of infection in arthritis. The incidence of the rarer foci such as the middle ear, female adnexæ, and so forth, can be found in Table II.

From these figures it is evident that the tonsils and teeth are by far the most common site of foci in infectious arthritis. This corroborates the observations of previous investigators. In this connection it is interesting to note that the average age of the onset of arthritis in patients with infected tonsils was thirty;

whereas the average age of onset in those with dental infection was forty-two.

Morbid Anatomy. In this series of cases there have been only two deaths. In neither of these cases were we able to procure autopsy material. From physical examination, however, and from a study of the radiographs it is obvious that chronic infectious arthritis is essentially an inflammatory and proliferative process. We use the term proliferative as employed by Nichols and Richardson[3] to describe a pathologic change in the joint structure which is primarily an inflammation of the synovial membrane and the periarticular structures. Because of the fact that many of the patients were seen early before bony changes had taken place, a large number presented only periarticular changes which were apparent on physical examination and also with the Roentgen ray, as a diffuse swelling of the soft parts around the joint. This periarticular infiltration is quite characteristic of the type of arthritis under discussion. Some of the more chronic cases showed bony changes particularly at the margins of the articulating surfaces. Occasionally bony spurs have been found with the Roentgen ray, but undoubtedly, in a large majority of the cases of infectious arthritis the *primary* change is in the synovial membrane and not in the articular cartilages. This is in sharp contrast with the degenerative type of arthritis which almost invariably *begins* as a destructive process in the bone and cartilage of the articular surfaces.

Symptomatology. Patients with infectious arthritis often date the onset of their illness from some disturbance of their physical equilibrium such as an acute infection, exposure to cold, a surgical operation, or a confinement. In taking the histories of patients we were interested in discovering any such predisposing factor which might have precipitated the arthritis. Twenty-nine patients gave a history of a preceding tonsillitis or sore throat; 24 had had a cold or influenzal attack just before the onset of arthritis; 10 others dated their joint symptoms from an attack of rheumatic fever. In 5 cases, arthritis developed after a surgical operation. A large number of patients gave a history of exposure to cold or damp surroundings. In 118 cases no immediate predisposing factor was demonstrable.

Chronic infectious arthritis is usually a polyarticular disease which may involve any joint in the body. It may develop suddenly or gradually. In the present series the onset was sudden in 119 cases and gradual in 81 cases. When the onset is sudden the patient may run an irregular fever, varying from 99° to 100° or even 101°. The disease is almost always migratory in its early stages, jumping about from joint to joint very much like rheumatic fever. After several attacks however, the joints chiefly affected become permanently injured and the process takes on a chronic character. The following table indicates the joints first involved.

TABLE III.—JOINTS INVOLVED.

Joint.	No. of times first involved.
Knee	38
Shoulder	25
Finger	22
Questionable	20
Feet	16
Wrist	15
Ankle	14
Back	10
Elbow	9
Hand	7
Toe	5
Hip	4
Arm	3
Spine	3
Heel	3
Leg	2
Neck	2
Thigh	1
Jaw	1

The knees were the joints first involved in only 19 per cent of the cases. This is in sharp contrast with the menopause type of degenerative arthritis in which the disease made its first appearance in the knees in 84 per cent of the cases.

Occasionally the disease limits itself to only one joint, but in the present study only 2.5 per cent of the cases were monarticular. The number of times each joint was involved is shown in the following table:

TABLE IV.—TOTAL NUMBER OF TIMES THE VARIOUS JOINTS WERE INVOLVED.

Knee	128	Toe	24
Finger	102	Heel	18
Shoulder	87	Knuckle	18
Wrist	74	Neck	15
Ankle	67	Arm	13
Feet	55	Heberden's nodes	12
Elbow	51	Leg	10
Hand	48	Thigh	6
Back	37	Jaw	4
Hip	33	Sternoclavicular	2
Spine	24		

The knees were the most common site of involvement; they were implicated in 64 per cent of the whole series. Fingers and shoulders were the next most frequently affected, 51 and 43 per cent respectively. It is interesting to note that Heberden's nodes occurred in only 6 per cent of the cases, which is in marked contrast with the menopause type of degenerative arthritis in which they occurred in 74 per cent of the series. Of the 102 cases in which the fingers were involved, 58 presented the fusiform finger joint, one of the characteristic features of infectious arthritis.

The patient with infectious arthritis is usually quite uncomfortable. In most cases there is considerable pain, particularly on motion. For this reason the patient is more apt to be seen early in the disease than is the victim of menopause arthritis which mainfests itself only as a stiffness of the joints, particularly in the early stages. Many of the patients complain of swelling of the joints affected, and sometimes there is redness and heat as well. As the disease advances, there is considerable disability due to pain on motion and weakness of the muscles from disuse. Unless the disease is checked in its course partial or complete ankylosis may occur in one or more joints.

Physical Examination. Typical cases of chronic infectious arthritis present certain constitutional signs that are striking. They are usually anemic, averaging about 73 per cent in hemoglobin; many of them appear chronically ill and undernourished; some of the patients present marked evidence of loss of weight, particularly those, in whom the disease has lasted for some time. Some of the early cases, however, show excellent nutrition and no anemia. Fever is uncommon when the cases are seen at the clinic but may be present at the onset of the disease.

The examination of the tonsils is naturally of great importance. Infected tonsils as seen so often in young adults may be large, red, and full of pus. Perhaps more frequently, diseased tonsils are small, congested, and partially buried. This type is more common in adults and in early middle age. Either one of these types may contain deep crypts from which pus or cheesy exudate can be expressed. In these cases the fauces of the tonsils are apt to be involved in the infection and present a congested cyanotic appearance. In addition to the infection of the faucial tonsils the patient may show a granular pharyngitis with hypertrophy of the lymphoid tissue.

The gums may show various grades of gingivitis. Pyorrhea may be mild or severe; localized or general. Apical abscesses are found only at the roots of dead teeth.

The examination of the chest is usually negative. We have not seen a single case of infectious arthritis that could be definitely attributed to pulmonary infection. Examination of the heart is usually normal but cardiac lesions are apt to be present in those patients that give a history of acute or subacute rheumatic fever. The abdominal findings are as a rule negative except in the small percentage of cases in which there is infection of the gall bladder or some other part of the intestinal tract. The genitourinary exploration of the male may reveal a swollen, boggy and tender prostate. In the female marked erosions may be found in the cervical mucosa.

In the early stages the joints affected usually present a characteristic appearance. There is more or less swelling of the soft parts and the overlying skin is warm and sometimes reddened. In some cases there is an increase in synovial fluid. The swelling is due for

the most part to the outpouring of inflammatory exudate into the periarticular structures. Tenderness is usually present and is most marked on the lateral aspects of the joints. Motion either active or passive is painful. In the early stages there is no crepitation.

In the later stages much of the swelling disappears. A certain amount of thickening may persist about the joint due to a new growth of fibrous tissue in this region. In the joint itself however the granulation tissue may become converted into adhesions which eventually lead to partial or complete fibrous ankylosis. In those cases in which proliferation of the perichondrium predominates bony ankylosis is apt to occur. Ankylosis is usually associated with considerable atrophy of the neighboring muscles. Sixteen of the present series showed fibrous ankylosis and 6 of the patients were found to have true bony ankylosis.

In this connection it is interesting to note that the longer the duration of the disease the more apt are we to find bony changes present. Only 23 per cent of the cases showed definite bony changes, and their average duration was four years, eight months three weeks, as contrasted with the average duration of two years, six months, in the cases which showed no bony changes. Swelling was present in 51 per cent of the cases. In the patients that are seen early there may be no swelling or bony changes present and the disease may be manifested solely by subjective sensations. In these cases examination of the joints reveals nothing abnormal except possibly slight tenderness on motion. Fusiform finger joints are a common finding in this type of arthritis and when seen are almost diagnostic. They occurred in 58 cases of our series.

Illustrative Case. The following case is a good example of chronic infectious arthritis:

H. S., a man, aged thirty-eight years, whose weight was 125 pounds and height 5 feet 7 inches, had had intermittent pains in the joints for the past twelve years. These pains skipped from joint to joint, especially in the attack which he had suffered eight years before and which had lasted for about one year. He has never had fever and never been confined to bed. At different times his joints have been swollen, red and hot. For the past five years he has had pain, swelling, and stiffness of both wrists. His condition is stationary at present. No history of sore throats or tonsillitis was elicited, but nine months prior to admission eight abscessed teeth were removed. Physical examination reveals a poorly nourished adult, male, 27 pounds underweight; considerable dental repair is present but no pyorrhea. The tonsils are red, ragged, and contain pus. Heart and lungs are normal; abdominal examination negative. Prostatic examination reveals nothing abnormal; examination of the sites of other foci is negative. Locally both wrists

are thickened, slightly tender and warm, and markedly restricted in function. Several fusiform finger joints are present. Wassermann test was negative on two occasions. Blood sugar, 115 mg., uric acid, 3.3 mg.; hemoglobin, 60 per cent; white blood cells, 11,200; polymorphonuclears, 71 per cent; lymphocytes, 25 per cent.

In this case the principal features of chronic infectious arthritis are present. An adult patient, considerably underweight, with marked anemia, gives a history of migratory involvement of the joints and presents upon physical examination polyarticular arthritis with swelling of the various joints and fusiform finger joints. In addition, foci of infection are present.

Laboratory Findings. *Bacteriology.* We have had no opportunity to take cultures from the infected joints themselves. Cultures from the various foci of infection corroborate in general the work of previous investigators. It is interesting to note that cultures from infected tonsils usually yield large numbers of hemolytic streptococci, whereas cultures from apical abscesses almost invariably give pure growths of Streptococcus viridans from other foci of infection either type of streptococcus may be obtained. One is forced to conclude from this that both Streptococcus hemolyticus and Streptococcus viridans can act as the etiologic agents in infectious arthritis.

Serologic Diagnosis. The complement-fixation test as advocated by Burbank and Hadjopoulos[4] has not been employed in this study. We are therefore in no position to criticize it as a diagnostic measure. On theoretical grounds, however, it would seem to be open to several sources of error. In the first place the authors assume that every case of arthritis is infectious in origin, a point of view which we think is untenable. Furthermore it is quite conceivable that an individual, who at any time had had a streptococcus infection of whatever nature, would have streptococcus-fixing antibodies in his blood as a result of such infection. Since it is extremely difficult to rule out the history of streptococcus infection in any patient the value of the test even when positive is open to question.

Blood Chemistry. In 14 cases the determination of the blood sugar was done. The average finding was 125.3 mg. which is slightly above the normal limit. In 16 patients the uric acid in the blood averaged 3.3 mg. The urea and creatinin in the blood were estimated in a few cases with negative results.

Basal Metabolism. Seven cases had basal metabolism determinations. The findings were entirely negative.

Diagnosis. The diagnosis of a typical case of infectious arthritis presents very little difficulty. The important features that differentiate this particular type from other forms of joint disease are the following:

1. It is more apt to occur in young people.

2. The migratory character of the disease is characteristic.

3. The affected joints are usually swollen and tender.

4. Infectious arthritis is prone to attack the metacarpophalangeal and proximal phalangeal joints.

5. Foci of infection can usually be demonstrated.

Differential Diagnosis. Infectious arthritis must be differentiated from subacute rheumatic fever, a distinction which is not always easy to make. In both conditions the patient may give a history of a preceding tonsillitis followed by an acute arthritis with fever and swelling of the joints. In rheumatic fever however, the temperature is higher, the sweating is more profuse and cardiac complications are frequent. The therapeutic test is valuable. Treatment with sodium salicylate or aspirin usually gives instant relief in rheumatic fever. In infectious arthritis these drugs are practically useless.

Menopause arthritis occurs in obese middle-aged women at or just after the menopause and attacks chiefly the knees and distal phalangeal joints. There is an absence of inflammatory swelling. It is not migratory and foci of infection are usually absent. It may be advantageous to draw a parallelism between these two outstanding types of arthritis.

TABLE V.—DIFFERENTIAL DIAGNOSIS.

	Infectious arthritis.	*Menopause arthritis.*
Average age at onset	Third and fourth decades	Fifth and sixth decades
Weight	Normal or underweight	Overweight
Blood	Low hemoglobin	Normal hemoglobin
Foci of infection	Usually present	Usually absent
Morbid anatomy	Inflammatory and proliferative changes	Degenerative changes
Joints involved	Any joint in body	Chiefly knees and fingers
Type	Migratory or progressive	Localized
Appearance of joints	Periarticular swelling	No swelling
Special signs	Fusiform finger joints	Heberden's nodes
Roentgen ray	Narrowing and clouding of joint space	Lipping of bony margins

The specific forms of arthritis as well as morbus coxæ senilis and senile arthritis present such characteristic features that there is little difficulty in distinguishing them from the infectious type.

Treatment. The method of procedure in the treatment of these cases has been: (1) The removal of all foci of infection; (2) vaccine therapy; (3) physiotherapy. Medicinal treatment has played practically no part in our therapeutic regime. In the clinic we have not employed foreign protein therapy intravenously for obvious reasons.

Tonsillectomy. Altogether 85 patients (42.5 per cent) in this series of cases were subjected at some time to tonsillectomy. In 9 of these the operation was performed twice. In all, 94 tonsillectomies were done. Strangely enough, 27 patients were subjected

to tonsillectomy before the arthritis made its appearance. In these cases obviously the tonsils were not the focus of infection. The following table shows the relationship of tonsillectomy to the duration of the disease:

TABLE VI.—RELATION OF TONSILLECTOMY TO DURATION OF DISEASE.

Duration of disease...	*No. of cases.*
Tonsillectomy before onset	27
6 months or less	18
6 months to 1 year	10
1 year to 2 years	9
2 years and over	26
Relation unknown	4
Total	94

Nearly half of the patients with chronic arthritis waited two years before having their tonsils removed.

Teeth were extracted because of apical abscesses in 21 cases. A considerable number of patients were treated for pyorrhea. Eight patients received prostatic massage and bladder irrigations. Five cases were treated for disease of the cervix. Four cases had infected sinuses punctured and irrigated. Only 1 gall bladder was removed and the middle ear received treatment in 2 cases. In a considerable number of cases the removal of foci was supplemented by colonic irrigations.

Vaccine Therapy. Vaccine therapy was used in the treatment of 39 cases. In only a few of the cases did this constitute the sole method of treatment. As a rule this form of therapy was used only after a thorough search for foci of infection. A polyvalent Streptococcus hemolyticus vaccine with a concentration of 4 billion organisms per cubic centimeter was used in 27 cases. The initial dose was as a rule 0.2 cc. The vaccine was administered subcutaneously twice a week until ultimately the patient received 1 cc. at each injection. Autogenous vaccines prepared from the deep crypts of the tonsils directly after their removal, were given in 7 of the cases. A polyvalent Streptococcus viridans vaccine was used in 2 cases and Bacillus coli and Staphylococcus aureus vaccines were used in 1 case.

Physiotherapy. Physiotherapy was used as an adjuvant in the treatment of almost every case. Baking, massage and diathermy were the methods of treatment most frequently employed. As a rule this treatment was not used during the period of active inflammation in the joints but was reserved for the resolution of exudates and the restoration of function.

Period of Observation. In this series of 200 cases, 57 patients were sent to the Clinic for diagnosis only; 143 received treatment. Of the latter group, 92 patients were under our observation for a period of time lasting from three months to three years. Thirty-

seven cases were treated less than three months and the duration of treatment in 14 cases is not known.

Results of Treatment. The duration of the arthritis when treatment is instituted is a determining factor in the results obtained. In the following table this relationship is clearly brought out.

TABLE VII.—RELATION OF DURATION OF ARTHRITIS TO RESULT OF TREATMENT.

Results of treatment.	No. of cases.	Average duration of disease when treatment started.
Recovery	20	1 year 1 month
Much improved	39	3 years 10 months
Improved	43	4 years 5 months
Unimproved	39	5 years
Died	2	1½ years and 3 months
Total	143	

It is clear that results in the treatment of chronic infectious arthritis depend as much on the duration of the disease as they do upon the therapy employed. The significance of this fact has not been sufficiently emphasized. It may be laid down as an axiom that cases seen within the first year of the disease have an excellent chance of recovery under suitable therapy and that cases which have lasted five years and over present almost insuperable difficulties in their treatment. It would be well for both patient and physician to realize that the treatment of arthritis no less than the treatment of tuberculosis should be instituted early in the course of the disease. The most painstaking search for, and removal of foci in late cases does not give the results that are obtained in cases that have lasted only six months or less. The following table shows the results of treatment in cases of less than six months duration:

TABLE VIII.—RESULTS OF TREATMENT IN EARLY CASES.

Total number of such cases	36
Cured	10
Much improved	11
Improved	8
Unimproved	6
Died	1

It is significant that 82 per cent of these cases were either cured or improved while on the other hand an analysis of the unimproved cases shows that the average duration of the disease when treatment was instituted was five years.

The duration of treatment in the unimproved cases averaged three months (most of them coöperated). Thirteen tonsillectomies were performed in this group without success. Extraction of teeth was done in 7 cases. Streptococcus hemolyticus vaccine was given in 6 cases. Prostatic massage was employed in 1 case and

most of the patients received physiotherapy. Failure to improve under treatment was undoubtedly due to the long-standing processes in the joints and the presence of secondary foci of infection.

Tonsillectomy. Of the 65 tonsillectomies that were done after the onset of arthritis only 29 were cured or showed improvement. It is only fair to state that 13 of the remaining 36 tonsillectomies were performed after the disease had been present for five years. In those cases in which the tonsils were the foci of infection and their removal was effected within the first six months of the onset of the arthritis our results have been uniformly good. It has been our experience that the full effect of tonsillectomy is not obtained until three to six months after operation.

Results of Extraction of Teeth. Of the 21 cases that had extractions done, 7 were cured, 3 much improved, 3 improved, and 8 unimproved. Sixty-two per cent of the series were cured or improved by this method of treatment.

Results with Vaccine. It is difficult to evaluate the role that vaccine played in the treatment of these cases, as it formed only a part of the general therapeutic régime. Our experience with Streptococcus hemolyticus vaccine has not shown uniform results. A few of the patients have responded favorably for a short time, but the vaccine itself seems to have no specific action and does not appear to be superior to any other foreign protein in its effects. Autogenous vaccine has been used in only 7 cases, with apparently marked improvement. But as these patients had all been subjected to tonsillectomy before the vaccine was employed it is difficult to separate the effect of vaccine from the end-results of tonsillectomy.

Physiotherapy. In our experience physiotherapy (radiant heat, 15–20 mm.; diathermy, 20 minutes, massage and passive movements, when indicated) has been a valuable aid in the treatment of infectious arthritis. It may act favorably in two ways, first, by accelerating the absorption or removal of exudates, second, by hastening the return of function in the partially ankylosed joints. It is obviously not indicated until after foci of infection have been removed.

Summary. 1. Infectious arthritis is primarily a disease of early adult life.

2. The tonsils and teeth are the commonest foci of infection.

3. In young people infected tonsils are responsible for a high percentage of the cases. In older patients infected teeth are more apt to be the etiologic factor.

4. The pathologic changes are of a chronic inflammatory and proliferative character, terminating often in ankylosis and deformity.

5. Clinically the disease manifests itself as a migratory, polyarticular affection of the joints characterized by swelling, pain, and stiffness of the parts affected. The fusiform finger joint presents the typical picture.

6. Success in treatment is dependent upon a relentless search for foci of infection, and their prompt removal early in the course of the disease.

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MYOSITIS OF RECTUS ABDOMINIS MUSCLES CONTRASTED WITH ACUTE INTRAÄBDOMINAL CONDITIONS.

By R. D. Leas, M.D.

CLEVELAND, OHIO.

(From the Department of Medicine of Lakeside Hospital and Western Reserve University, Cleveland, Ohio.)

A search of the literature on myositis of the abdominal muscles reveals very little which may be interpreted as a differential diagnosis between this condition and those of acute intraäbdominal origin. In this location myositis assumes considerable importance because of its possible confusion with suspected intraäbdominal disease. There is a certain percentage of cases with acute abdominal pain in which myositis is the causative factor, as shown by examination and the response to salicylates. The purpose of this paper is to review the symptoms of abdominal myositis in contrast to those of intraäbdominal conditions and report 2 cases illustrating the typical syndrome. A theoretical discussion of the probable cause of pain in myositis and perimyositis is also given.

The earliest and most complete consideration of myositis from this standpoint was given by Hoover.[1] He pointed out that an inflamed muscle, unlike most structures which are tested for the seat of pain, gives no pain on functional employment if the inflammatory process is within the muscle sheath. The lack of pain on functional employment is explained by the structure of the muscle. It consists of a sheath containing a semiliquid substance in which pressure is transmitted equally in all directions during activation in the same manner as pneumatic or hydrostatic pressure. Since pressure is applied in this manner within the muscle sheath there can be no distortion of its component parts. However, when an inflamed muscle is palpated or stretched, there is distortion of its structure and pain results. The same principle may be illustrated in the case of a subcutaneous abscess. There may be pain due to tension on the walls of the abscess from within and to barometric pressure on the skin surface, but it is not nearly so intense as that produced by distortion of the walls by manipulation.

It is to be noted that perimyositis gives pain on activation of the involved muscle. In such a case adhesions between the sheath and surrounding tissues give opportunity for distortion of the inclosed muscle. Friction between sheaths of contiguous muscles, the seat of perimyositis, may also be the cause of pain. The mechanism of pain production in such pathological conditions is not entirely clear. It cannot be due to the same sort of intense stimulation of nerve ending, for instance, as results from the application of a hot object to the skin surface. Therefore since thermal stimuli can be disregarded it must in all probability be due to mechanical factors. A friction rub immediately suggests the movement of one roughened surface over the other but this alone cannot explain pain nor on the other hand does inflammation of the otherwise smooth surfaces explain it. It seems logical that as a result of inflammation there is a distortion of tissues resulting in compression and stretching and thereby irritation of nerve endings. A normal muscle may be stretched within limits without pain, but if a constant traction is maintained for a long period of time, pain results. Therefore it seems essential to include the time factor as well as distortion in the production of pain.

There are cases of myositis in which there is complaint of some pain on activation, but not nearly as much as on mechanical distortion by palpation or stretching. It has been observed that such cases have had palpable masses in the muscle which varied in size from a small pea to large tumors, 5 to 6 cm. in width and extending transversely across the muscle. One patient had such areas in the upper part of both gastrocnemius groups, which were painful when the muscles were activated and also when at rest, but the pain was accentuated to a marked degree on stretching or palpation. The difference between such a case and one in which nodules are not palpable and there is no pain on activation is probably a matter of degree and duration of involvement. A small area of inflamed muscle cannot of itself produce much distortion, but a large tumor may so disturb the structural units of the muscle that pain becomes a constant symptom even when the muscle is relaxed. When the shoulder, neck and back muscles are involved the problem of diagnosis is much simpler than in the case of the abdominal group. The procedure in examining the latter group is first to palpate the abdominal wall thereby determining the presence or absence of rigidity, muscle spasm, and tenderness. The patient is then asked to bear down and the abdominal wall is palpated while under tension. If peritonitis is the causative factor the pain on palpation will be less in this than in the first procedure, and if myositis is the cause it will be accentuated.

In addition to this finding a sensory examination is of importance. There is never any disturbance of sensation of the skin overlying a muscle, the seat of myositis, but there is a change over an area of peritonitis. This latter fact was pointed out by Gammon[2] in 1912

when he demonstrated sensory disturbance of the skin over an acute appendicitis. He found tenderness on pressure over the appendix, but also a diminished sensibility to heat, cold, and the vibration of the tuning fork and attributed this to the inhibiting effect of visceral pain on other sensations in the same segment of the spinal cord. These findings were constant in cases of acute appendicitis when seen early in their course. If pain had subsided in such patients the sensory disturbances had also disappeared and operation showed a gangrenous or suppurating appendix. The explanation offered in such a case was that engorgement or gangrene had rendered the visceral peritoneum anesthetic which effectively blocked sensation to the cord and thereby removed the inhibitory influences on the sensations of heat, cold and pallesthesia to the segmental distribution of the skin. The same mechanism resulted in a diminution of pain by the application of an ice bag over the appendix which by intense stimulation of the skin inhibited pain from the appendix which was in the same segmental distribution. Thus, since inflamed peritoneum gives disturbed sensation, unless acute engorgement or gangrene is present, and myositis never gives such findings, sensory disturbances become an important factor in differential diagnosis.

Two cases have recently come under our observation, one with symptoms suggesting acute cholecystitis and the other acute appendicitis, both of which proved to be acute rheumatic myositis of the rectus abdominis muscles. A survey of the records of the Lakeside Hospital shows only 3 more cases which were undoubtedly of the same type. We do not consider this an indication of the extreme rarity of the condition, but rather failure of recognition in perhaps many more cases. For this reason a report of 2 typical cases may be of value.

It will be noted that the diagnosis in these cases was based on the following findings:

1. Activation of the rectus muscle was painless.
2. Stretching of the affected muscle caused exquisite pain.
3. Palpation of the relaxed muscle gave little pain, but of the activated muscle a considerable degree of pain.
4. There was no disturbance of sensation over the affected areas.
5. The administration of salicylates gave relief in a very short time.

Case Reports. CASE I.—M. L., a female, aged sixteen years, five days prior to admission had a dull aching pain in the right lower quadrant of the abdomen and also in both knees and shoulders. There was no nausea, emesis or diarrhea, but there was anorexia.

Past History. There had been an attack of acute rheumatic fever one year prior to this admission but, in the intervening period, there had been no symptoms of myocardial insufficiency. There

had been only one menstrual period, but there was no history of exposure to venereal disease.

Physical Examination. The temperature, pulse, and respirations were respectively 39.4°, 104 and 24. Both knees were swollen and tender with an elevation of the local temperature. Palpation of the relaxed abdominal wall revealed no muscle spasm and only a moderate degree of tenderness over the lower half of the right rectus muscle. However, when the muscle was stretched or activated, palpation gave very severe pain. There were no disturbances of sensation over the painful area. Rectal examination was negative. The cardiovascular system gave the findings of a well-established aortic insufficiency.

Laboratory Findings. On admission, January 10 at noon, the white blood cell count was 11,900. At midnight it was 10,800, and at 5 A.M. the next morning 11,600. A differential blood count showed 80 per cent polymorphonuclear leukocytes. The urine was negative for blood and showed only an occasional pus cell. A blood culture gave no growth in forty-eight hours.

Course. Cincophen was begun at 6 P.M. on January 10, in doses of 20 gr. every three hours and discontinued when nausea and emesis resulted at 9 A.M., January 11, when a total of 80 gr. had been given. The symptoms had cleared up so completely that the patient refused to stay longer than three and a half days, at which time, however, there was no tenderness over the right rectus muscle. The temperature fell to normal in twelve hours and continued normal.

Diagnosis. Subacute rheumatic fever, rheumatic myositis, chronic endocarditis with aortic insufficiency.

CASE II.—W. R., a man, aged forty-two years, six months prior to admission began noticing periodic attacks of dull aching pain in the epigastrium, not related to meals and with no associated nausea, emesis or eructation of gas. The appetite remained good. Two weeks prior to admission there was an onset of one and then periodical attacks, which involved the entire upper abdomen. On this occasion the pains were so severe that relief could not be secured without flexing the thighs on the abdomen. There was no gastrointestinal disturbance of any sort, and no constipation or abnormality of stools. There was no urinary disturbance and no fever. The patient had worried considerably and had lost about 15 pounds.

Past History. Entirely negative.

Physical Examination. The temperature, pulse and respirations were normal. The patient was lying in bed with thighs partly flexed on the abdomen. There was no icterus. The heart and lungs were normal. Abdominal examination showed no distention, visible peristalsis, palpable organs, tumors, or free fluid. The maximum points of tenderness were: (1) In the left lower quadrant

at the outer border of the rectus, 3 cm. below the umbilicus; (2) near the costal margin in the mid portion of the rectus muscle on both sides. Deep pressure gave muscle spasm and some pain over these areas, but stretching and distortion of the activated muscle very severe knifelike pain. There were no sensory disturbances. The prostate was slightly enlarged, but rectal examination was otherwise negative.

Laboratory Data. Roentgen ray plates of renal and gall bladder regions showed no calculi. The white blood cell count was 8000. The urine was negative and blood plasma not icteric.

Course. In a few hours after admission the patient was started on a course of cincophen, 15 gr. every three hours. Twenty-four hours later after 150 gr. had been given there was almost complete relief from abdominal pain and the patient had the first night of undisturbed sleep for two weeks. At this time palpation of the abdomen failed to elicit muscle spasm, but there was still slight tenderness to firm pressure midway between the umbilicus and xiphoid process. Activation gave no pain, but there was slight pain with stretching of the muscles a slight degree. During the next four days 640 gr. of sodium salicylate was given and the patient was discharged free of symptoms and signs.

Diagnosis. Myositis of rectus abdominis muscle.

Summary. 1. Two cases of myositis of the abdominal muscles are reported.

2. The literature on rheumatic myositis is reviewed.

3. The points in differential diagnosis between myositis of the abdominal muscles and intraäbdominal conditions are contrasted.

4. The probable cause of pain in myositis and perimyositis is discussed.

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THE MANAGEMENT OF THE CIRCULATION IN MYXEDEMA.

By George P. Pratt, M.D., F.A.C.P.,

and

H. B. Morton, M.D.,

omaha, nebraska.

(From the Medical Department of the University of Nebraska.)

Articles in the recent literature by Fahr,[1] Christian[2] and Willius[3] have prompted us to the further study of the subject. Fahr concludes there are definite objective signs and subjective symptoms

of heart failure which are characteristic of myxedema and which do not respond to digitalis and rest but are relieved by thyroid medication. He cites a case and recommends thyroid extract for cardiac decompensation in myxedematous patients. Christian, stimulated by this article, reviewed the subject with a study of several cases and summarized as follows: "Patients with myxedema frequently have symptoms and physical signs of circulatory insufficiency. This whether due to thyroid hypofunction or a coincidental disturbance, must be taken into account in planning treatment, because, when thyroid is given in sufficient amount to elevate metabolic rate and cure myxedema manifestations, increased work is thrown upon the heart. This burden is increased if anemia of marked degree is present. To meet it the heart must be able to respond by increasing its work. To do so may require digitalis and other cardiac therapy prior to or during the giving of thyroid extract. To neglect the circulatory element in the treatment of the clinical situation may result in discomfort or disaster from circulatory failure." Willius in a review of 162 cases thinks a definite cardiac syndrome characteristic of myxedema does not exist.

The case which we are reporting with autopsy records and conclusions may serve as a case in point and is further justified by adding to the literature data concerning multiple thrombus formation in the larger bloodvessels.

Case Report. Mrs. G. M., housewife, aged forty-five years, widow, was admitted to the University Hospital (No. 18299) November 7, 1925. During childhood she had measles and whooping cough; at the age of ten years she suffered an attack of typhoid fever, and one year later rheumatism at which time she was confined to bed for four months, and suffered with stiff, painful joints intermittently for the four years following. Her menstrual periods which began at the age of seventeen years had always been scanty and quite irregular. The last menses were in May.

At the age of eighteen years relatives noticed she lacked ambition, her speech became slow, and she tired easily. Her features gradually changed, the face broadened, the eyes and face became puffy, the hair grew coarse, and the skin was thick and scaly. A hypothermia developed and the patient chilled easily. She could work in the field on a hot day quite heavily clothed without perspiring. This condition continued to the present time and although several doctors were seen for miscellaneous ailments, none made a diagnosis of myxedema, and no therapy was instituted. The myxedema had been progressing for twenty-seven years. She more recently developed shortness of breath on exertion, sinking spells, and pain through the upper abdomen radiating to the chest and shoulders rather definitely, but more marked on the right. The pain was

paroxysmal but on account of the apathy its exact nature could not be determined.

On physical examination of the patient, all the characteristic findings of a well-advanced case of myxedema were present and will not be considered in detail. The apex beat was found in the anterior axillary line at the sixth interspace. There was a systolic murmur present, best heard at the apex. The abdomen was slightly tender along the right costal border. The liver was barely palpable. The external genitalia were poorly developed and the uterus was of the small infantile type. The reflexes were sluggish. The blood pressure was systolic, 110; diastolic, 72; pulse rate, 72; respirations, 22; temperature subnormal.

The urine was negative; blood nonprotein nitrogen, 30 mg.; blood sugar, 118 mg.; red blood cells, 3,700,000; hemoglobin, 70 per cent; white blood cells, 6000; blood platelets 230,000; clotting time six minutes. The basal metabolic rate was − 30. The Roentgen ray examination of the teeth showed deep pyorrhea with some bone absorption. The heart shadow was enlarged 4 + to the left and right and the gastrointestinal radiograms were negative.

A diagnosis of myxedema and cardiac hypertrophy with slight decompensation was made, and on November 10 the patient was put on a beginning dose of thyroid (5 gr., t. i. d.) put to bed, and kept under close observation. On the fifth day, in spite of the complete rest, it was evident that the decompensation was increasing and edema appeared over the sacrum. The thyroid extract was decreased to gr. i, t. i. d. The signs of hypothyroidism became less marked. The heart action seemed better and the edema had disappeared from the sacrum. November 21, the thyroid was increased to gr. ii, t. i. d. On November 26, the patient complained of pain in the left side of the neck. An examination revealed a thrombus in the left external jugular vein extending upward for about an inch. The temperature was normal. Several days later the left forearm and hand became numb, cold, bluish and very painful. The pulse could not be felt at the wrist but was present in the brachial artery. A line of demarcation had formed about midway up the forearm. The temperature was normal; white blood count 15,800; the blood cultures repeatedly were negative. December 2 the patient had a slight febrile reaction (100°), the respirations were increased and on examination of the left lung revealed rales and evidences of consolidation in the right lower lobe. The thyroid medication had, of course, been stopped and digitalis therapy instituted. The lung lesion gradually cleared up. A dry gangrene with a definite line of demarcation 4 inches below the elbow had developed in the left forearm. On December 8, there was a left femoral thrombosis followed the next day by a right femoral thrombosis, and on December 10 a thrombosis of the superficial veins on

the medial aspect on the right arm, and in the right external jugular which receded in a few days. By December 26 the jugular veins had softened, the swelling left the legs, and the general condition was much better, and the left arm was amputated by Dr. Jonas just below the elbow under local anesthesia. The stump healed slowly.

The patient remained in the hospital until her death from cardiac failure April 24, 1926. During this time she became markedly decompensated with the slightest effort, or with the institution of thyroid therapy which would be started at intervals and on account of the increase in cardiac symptoms would be discontinued.

Autopsy. An extract of the autopsy record made by Dr. Miller of the pathology department is as follows:

The body is that of a well-nourished and fairly well-developed white woman. The hair is thin, dry, and coarse and the skin over the entire body is thick, dry and scaly. There is no hair in the axilla or pubic regions. The left arm has been amputated just below the elbow and the stump is well healed. The right lower extremity is swollen. The teeth are separated.

Grossly the thyroid weighs 9 gm. and is of the consistency of connective tissue. The sectioned surface reveals small irregular masses of mahogany-brown tissue. The connective tissue of the neck and the vascular compartments of each side are firm and dense. Both external jugulars are thrombosed but soft and pliable. The internal jugulars and carotid arteries are patent. There is an old, firm thrombus in the left brachial artery about 6 cm. from the stump. The veins of the left arm are patent.

The heart weighs 475 gm. The right auricle is filled by an old brownish-colored pliable clot. There is a large mural thrombus in the tip of the left ventricle. The coronary vessels are sclerosed and almost occluded near their orifices. The larger branches, however, are free from thickening and other signs of sclerosis. The right ventricle is about twice normal thickness. The endocardium is thickened and light colored. That of the left ventricle is unusually firm and thick, and in underlaid by a light-colored, firm zone of muscle tissue.

Microscopically, the sections of the veins show them to be filled with organized and canalized thrombi. There is considerable damage to the wall of the vein and the perivenous tissue scarred. The thrombus of the brachial artery is organized and canalized. There are no signs of infection in the arterial wall. The mural thrombi of the heart are partially organized. There is necrobiosis of the heart muscle near the endocardium of the left ventricle. Connective tissue is increased, dense and hyalinized. There is no sclerosis of the branches of the coronary vessels. The aorta and large vessels contain typical changes of arteriosclerosis, senile type. The thyroid is almost completely destroyed by slowly progressing,

destructive change. The colloid is small in amount and that present is coarsely granular, and being attacked by phagocytes. There are only a few nests of acini composed of large epithelial cells with dense nuclei. The cytoplasm takes a dense eosin stain. The acini apparently shrink in size, the cells become deranged, degenerated and die. At the periphery of the small epithelial masses there is a dense leukocytic infiltration in which lymphocytes are arranged in follicle formation. Beyond this zone of the gland is old, dense, connective tissue in which there are a few infiltrating leukocytes of all types. Sections of all viscera show many masses of streptococci filling small arterioles. There is no reaction around them.

The section of the skin contains one hair and no sebaceous glands. The sweat glands are small and atrophic. The corium stains faintly and is edematous. The arterioles of the skin are thick and vacuolated. There is a diffuse and moderate infiltration by leukocytes, most of which are polymorphonuclear.

Conclusions. It is quite evident that thyroid medication used in the treatment of myxedema in sufficient dosage to cure myxedema manifestations and raise metabolism will throw sufficient strain on the circulation to increase a cardiac decompensation. We think the damaged heart should be built up with cardiac therapy before thyroid extract is administered.

In the case reported the changes in the heart muscle are believed to be the result of coronary sclerosis. In this instance the sclerosis is in the main branches only. In spite of the attack of rheumatic fever at the age of eleven no active heart lesion of rheumatic fever was found, and the principle tissue changes of the heart do not suggest it. The sclerosis may be due directly to thyroid insufficiency.

The mural thrombi are the result of myocardial and endocardial damage. The thrombus in the brachial artery is the result of an embolism from the mural thrombi with the following organization and canalization. The venous thrombi are not explained. They may be due to a slowing of the circulation and, as is commonly the case, form in larger vessels due to eddying of the blood at the periphery. In the literature, the external jugular veins are the usual site of formation of this type of thrombus. The damage to the venous walls may be interpreted as the result of infection, but it may also be the result of the reaction accompanying thrombosis.

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STUDIES IN URTICARIA. I. WHEAL PRODUCTION THROUGH INTERNAL CHANNELS.

By Abraham Walzer, M.D.,

and

Matthew Walzer, M.D.,

new york city.

(From the Department of Bacteriology and Immunology, Division of Immunology, Cornell University Medical College, and the New York Hospital, and from the Jewish Hospital of Brooklyn.)

Introduction. It is now universally accepted that the wheal, the clinical manifestation of urticaria, is an affection of the skin, mediated by principles derived from two different sources, external or local, and internal or constitutional. Wheals of the former group are produced by the bites or stings of various insects, and by various physical, chemical, or traumatic agents. Among the internal or constitutional causes may be mentioned hypersensitiveness to foods, drugs, and sera, intoxications, infections, metabolic and nervous disturbances, etc.

Up to the present time, the wheal of external origin has been the basis of investigation in most of the experimental studies of the skin manifestations of urticaria. Wheals have been produced locally on the skin, by applications of various physical, mechanical, and chemical agents, and also by intradermal injections of various substances. Probably the earliest record of such work is that of Philippson.[1] Working both on animal and human skins, he produced wheals with morphin, codein, peptone, and so forth, which he inserted into the skin by means of fine capillary tubes. His work was confirmed by Török and Hári[2] who used, in addition, a number of other drugs. Jadassohn and Rothe[3] experimented with morphin wheals produced by the scarification method. Eppinger,[4] using the same technique, was the first to employ histamin in the production of wheals. Sollmann and Pilcher,[5] by means of the scarification and mucuna* methods, produced wheals with a number of drugs, including histamin, morphin, peptone, and so forth. Lewis and Grant[6] made an admirable study of wheals produced by pricking the skin upon which a drop of histamin solution had been placed.

The intradermic method of wheal production was adopted by Pilcher and Sollmann[7] in their study of morphin wheals. They concluded that race (white or black), age, and sex, did not influence

* Mucuna ("Cowhage;" "Cowitch") consists of the fine stiff hairs of a leguminous seed pod. When gently rubbed on the skin, pruritus with or without erythema is produced. Rubbing the solution of the drug on this area results in the formation of a wheal.

either the size or severity of the reaction. Pilcher[8] studied wheal formation by the intradermal injection of codein in a series of infants with nephritis, cardiac compensation, leukemia, cretinism, myxedema, scleroderma, and[9] in rickets and spasmophilia. Except in edematous and sclerotic skins, the wheals did not vary.

Mechanical and physical agents, such as stroking, heat, puncture, scratching, suction, and so forth, were employed for wheal production by Ebbecke,[10] Lewis,[11] and Lewis and Grant.[6] These workers not only produced wheals, but made some interesting observations on certain physiologic factors affecting the wheal in its formation.

It is to be noted, therefore, that up to the present writing, all investigators have produced wheals by the direct application to or into the skin of various agents, either chemical, physical, or mechanical. The experimental production of wheals through internal channels had not, as yet, been accomplished. The writers have, however, devised a technique, based on an immunologic principle, by which such wheals may now be produced at will, on the skin of almost any individual. The mechanism of this reaction, it is believed, simulates that of an urticaria of internal origin. It is probably a reproduction of wheal formation as it occurs in urticaria due to food hypersensitiveness, the type most commonly encountered by the clinician.

Immunologic procedures for wheal production have not previously been employed to any considerable extent in the experimental study of urticaria. The reactions described by Duke[12] can hardly be considered of such nature, since they are the result of the direct action of physical agents, such as light, heat, cold, freezing, and so forth, on a sensitive skin. The usual skin tests for hypersensitiveness, which are now generally employed, either with the scratch or intradermal method, also furnish wheals of external origin, but necessitate for their production an additional constitutional factor in the form of skin hypersensitiveness. This immunologic method of wheal production, however, has not been extensively utilized in urticarial studies.

The immunologic principle on which this investigation is based is an outgrowth of the work of Prausnitz and Küstner,[13] De Besche,[14] Coca and Grove[15] and others. These workers have shown that an intradermal injection of certain hypersensitive patients' sera into the skin of almost any individual, temporarily sensitizes that site to the same substance to which the patient is sensitive. A positive reaction, a wheal, can be elicited by the intracutaneous test of these sites with the offending substances.

It was while working on one of the phases of this question that one of the writers (M. W.)[16] found the basis for the present study. It was observed that, with the sera of certain food-sensitive patients, the positive skin reaction, the wheal, could also be elicited at a passively sensitized site in most individuals by the ingestion of the

offending food.[17] In other words, by injecting certain hypersensitive patients' sera into the skin of the average individual, and, under proper conditions, feeding him the specific offending food, a wheal can be elicited at the sensitized site.

This specific wheal-inducing property is not present in the sera of all hypersensitive patients. To date, only four such sera have been found. These were obtained from patients who give very marked skin reactions to certain foods by dermal testing, and clinically manifest their sensitivity by asthma and skin lesions. The history of two of these patients is here submitted.

CASE I.—M. K. is a male child, aged two and a half years. The father has asthma. The child has had asthma since he was one and a half years of age, and has had "eczema" or "hives" more or less constantly since he was three weeks old, but is worse in the summer. The asthma attacks occurred at least once a month, lasting two or three days, preceded and accompanied by coryza and rhinitis. During the attacks the skin condition became much worse and the body was covered with a diffuse erythema, wheals, and circumscribed edematous areas, and was markedly pruriginous. Between the attacks, the child showed a generalized eruption of numerous discrete pinhead to pea-size pink papules, many with scratched off tops. Some were secondarily infected from scratching.

On direct skin testing, positive reactions were obtained with cereals, egg, chicken, lamb, mustard, flaxseed and nuts. Of these the egg reaction was found to be the most significant. The serum of this case was the one employed in the subsequent studies of wheal production by egg ingestion.

CASE II.—J. M. is a female child, aged five years. There was no family history of hypersensitiveness. She was breast-fed, and at three months of age, developed "eczema" of the face, which lasted about three months. It promptly cleared up following local treatment and the elimination of fish, sweets, cream and chocolate from her mother's diet. When the child was about a year old, her mother noticed that mere contact of the child with fish produced a violent attack of urticaria. Fish in every form was therefore excluded from the diet. Asthma developed about two years ago, but attacks have been at long intervals, and usually following an acute bronchitis.

On direct skin testing, the patient gave very marked positive reactions to all fish and shell fish. The serum of this case was the one employed in the subsequent studies of wheal production by the ingestion of fish.

Technique. 1. *Preparation of the Serum.* To obtain serum, vein puncture is employed, under the usual aseptic precautions. The blood is drawn and mixed with a sterile citrate solution, to yield a

final 1 per cent concentration of the citrate. Instead of the citrated solution, the blood may be defibrinated by whipping. After it is rapidly centrifuged, the serum is removed, and then passed through a Berkefeld filter for sterilization. The serum so obtained may be used in full strength or in various dilutions. If bottled under sterile precautions (without preservative) and kept in the ice box, it retains its potency for more than six months.

2. *Local Passive Sensitization of the Normal Skin.* The skin site on the subject chosen for study is cleansed with alcohol, and $\frac{1}{20}$ to $\frac{1}{50}$ cc. of the sensitive serum, concentrated or in dilution, is injected intradermally, with the technique employed in the usual intradermal skin tests. Sufficient time is then allowed to elapse for complete disappearance of all signs of irritation, resulting from the trauma of the injection. A control, by the intradermal injection of any serum not sensitive to the specific offending food, may be employed on another site, using the same technique. It is important that the food with which the subject is to be tested should be excluded from his diet on the day of sensitization.

3. *Induction of the Wheal.* The wheal is induced by feeding the specific offending food. This is best accomplished after an abstinence from food for a period of six to eight hours, and is therefore usually most convenient in the morning, the subject having been locally sensitized on the previous day.

The offending food should be taken raw. With the egg serum, one egg, well-beaten, slightly flavored to taste, is usually employed. With the fish serum, about 50 gm. of raw salted herring is ingested. Changing the nature of the food by heating, boiling, baking, canning, and so forth, may diminish or prevent the reaction.

Within three minutes to two hours after eating the offending food, a wheal, the typical characteristic phenomenon of urticaria, forms at the sensitized site. Pruritus is usually the first symptom, soon followed by an erythema, and then the edematous wheal gradually develops. The time of onset, size, and intensity of the reaction is variable with the individual, and depends upon several factors, the chief ones of which are: (1) The amount, dilution, and nature of the sensitizing serum employed; (2) the ability of the subject to accept passive transfer of local sensitivity (about 90 per cent of normal individuals;[17] (3) the ability of the subject to absorb certain incompletely digested or raw proteins from the digestive tract (about 90 per cent of normal individuals[17]).

The reaction is a specific one. It develops only at the passively sensitized site, and only after the ingestion of the specific offending food. One wheal formation usually completely desensitizes the site. All control sites sensitized at the same time with other sera remain unaltered. Passively induced local sensitivity may persist from several days to a month of more[15] provided the offending food is excluded from the diet.

The reaction has been elicited in more than 90 per cent of over 100 subjects tested to date. The complete reaction, with all its variations in time of appearance, size, intensity, duration, and all other factors concerned in its development, both in normal and abnormal skins, will be the subject of subsequent communications. The reaction as an index to specific protein absorption is also being investigated, and these results will be published at some future date.

Discussion. The technique, which has just been described, involves an entirely new principle for wheal production in the study of urticaria. It reproduces at will, in almost any individual, the wheal of a constitutional urticaria in a natural way. The factor which induces the formation of the wheal gains access to the sensitized site in its natural form, and through natural channels.

The complete unaltered development of the wheal may be studied in its progressive stages from its onset with pruritus, then erythema, and finally, wheal, together with its retrogressive changes to normal. There are no local traumatic changes at the sensitized site immediately preceding the reaction, which may mask the early symptoms of the developing wheal. Local sensitization may be performed days or weeks before the offending food is eaten, so that any slight traumatic changes that may be produced at the localized site by sensitization have completely disappeared before the wheal is produced. This is in contrast with the older methods, which depend on some form of immediate and local excitation for wheal production.

Another advantage of the technique presented is the fact that it is harmless. With it, any number of wheals may be produced simultaneously on one subject. In the thousands of times that wheals have been produced in more than a hundred subjects irrespective of age, even in infants, there have been no mishaps or untoward results. This method eliminates the dangers of cumulative action or intoxication which accompany the use of powerful agents, such as morphin, histamin, and so forth in wheal production. It also makes unnecessary the employment of hypersensitive patients as subjects—a procedure which is always accompanied by the possibility of a constitutional reaction when the patient is tested with the specific offending antigen.

The single disadvantage in the entire procedure is the difficulty in finding the serum. Once the proper patient has been secured, however, serum may be taken from time to time and a generous supply assured.

Summary. 1. A summary of the previous work on experimental urticaria is presented, showing that all previous methods of wheal production employed various physical, mechanical, and chemical agents, locally applied, to produce a wheal.

2. A new technique for wheal production, based on immunological principles, is herewith presented. After passive sensitization of the

normal skin by the injection of serum from a hypersensitive patient, the wheal is produced at the site of injection by feeding the specific offending food.

3. The reaction is of internal origin, and results in a wheal which, to all appearances, simulates that of a constitutional urticaria.

4. Other advantages of this method of wheal production over those previously employed are presented and discussed.

For assistance in obtaining much of the above information, the writers are indebted to their colleagues, M. Brunner, H. Sussman, S. J. Wilson and S. Kramer.

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REVIEWS.

GOITER AND OTHER DISEASES OF THE THYROID GLAND. By ARNOLD S. JACKSON, M.D., of the Jackson Clinic, Madison, Wis. Pp. 300; 152 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $10.00.

THE author of this book, a devout follower of the Mayo Clinic School, has presented a treatise on the subject of diseases of the thyroid gland for the practising physician and particularly for the surgeon, based upon experience gained in the treatment of a large series of cases. The book is written almost in the semiconversational style of a surgical clinic, and is characterized by straightforward statements on diagnosis and treatment, in which indications for and against the use of iodin figure quite prominently. A simple working classification of diseases of the thyroid is presented in which the relatively new concept of "iodin hyperthyroidism" is given an important place.

Although it is primarily intended to be a practical treatise on diagnosis and treatment, one wonders whether in attempting to attain this difficult ideal the author has not been a trifle too didactic. Another criticism which might be raised is the relatively small space allotted to some of the important aspects of the normal gland. For instance, that very slightly over a single page should be allotted (in a work of about 300 pages) to the subject of the normal histology of the gland, seems a trifle scant; if we bear in mind the warning which Virchow expressed many years ago, and which indeed has been well borne out, that in order to gain a true conception of the structure of pathological lesions of the thyroid, the extreme lability of structure of the normal gland should be emphasized.

The book is, however, an important and useful publication and will undoubtedly fulfil the purpose for which it was written.

J. P.

SURGICAL ANATOMY OF THE HUMAN BODY. VOL. I. By JOHN B. DEAVER, M.D., SC.D., LL.D., F.A.C.S. Second edition. Three volumes. Pp. 551; 124 illustrations. Philadelphia, P. Blakiston's Son & Co., 1926. Price $12.00 each volume.

THIS, the second edition of *Surgical Anatomy* should warrant as great a reception as was given the first. The character of the

subject matter is such as to demand accuracy in description and detail, which accuracy is easily checked up by comparison with the standard works on anatomy. In this respect the book is beyond reproach. The illustrations are excellent, beautifully finished and serve as accurate reproductions. The fact that they are relief in character adds much to their value. The work is well edited, and the diction does much to relieve the reader from stereotyped style so commonly seen in books of this sort.

The author very properly in his preface gives unstinted praise to those who helped in the production of this work, a credit to all concerned.

The volume is attractively prepared with a splendid quality of paper and a good binding. E. E.

MODERN METHODS OF FEEDING IN INFANCY AND CHILDHOOD. By DONALD PATERSON, B.A., M.B. (EDIN.), M.C.R.P. (LOND.), Physician to Out-patient Department, Hospital for Sick Children, and Physician to the Infants' Hospital, Westminster; and J. FOREST SMITH, M.C.R.P. (LOND.), First Assistant to the Clinical Unit, St. Thomas' Hospital, and late John and Temple Fellow in Diseases of Children, St. Thomas' Hospital. Pp. 106; tables in text. New York: Paul B. Hoeber, Inc., 1926.

THIS is a monograph on infant feeding adapted for ready use by the general practitioner. Breast feeding is admirably considered, in its normal management and in the surmounting of the difficulties which arise in many cases. Artificial feeding is discussed according to accepted present-day ideas. The authors give more attention to prepared milks and proprietary foods than do most American writers. The use of special formulas, such as lactic acid milk, protein milk, thick cereal mixtures and butter-flour soups deserves more detailed discussion. J. S.

THE DIABETIC LIFE: ITS CONTROL BY DIET AND INSULIN. By R. D. LAWRENCE, M.A., M.D., Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Second edition. Pp. 167; 11 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $2.50.

OF the various small diabetic manuals intended for both doctor and patient which have appeared in the last few years, this little volume is the best that has come to our attention. There is much in it that may be difficult for the patient to grasp at the first reading,

but the practitioner will find it all the more valuable. The only objection that occurs to a conservative is that the ration unit used in the working diet is rather high in fat, having a ketogenic-antiketogenic ratio of 1.62, as opposed to 1.5 top limit, as advised by Woodyatt. The popularity of the book is attested by the call for a second edition within a year of the first. R. K.

BRAIN AND HEART.—By GIULIO FANO, of the Royal University of Rome; translated by HELEN INGLEBY. Pp. 142; 19 illustrations. New York: Oxford University Press, American Branch, 1926.

Brain and Heart, a small volume, is a collection of lectures which were given before students who desired to learn of the author's investigations and scientific views. Because of this request, the style is almost autobiographical and is charmingly so.

The subject matter is concerned with discussions of "living matter," "some relations between inhibition and will" and "excitability and automatism." Interspersed among statements of scientific views, or of experimental data, are remarks so characteristic that one gains a conception of personality, a scientist, an artist, a man of letters. The translator has succeeded remarkably well in maintaining this personality as well as translating the facts, none of which are essentially new. J. S.

PATHOLOGY AND TREATMENT OF THE INFLAMMATORY DISEASES OF THE NASAL ACCESSORY SINUSES. By DR. M. HAJEK, of the University of Vienna. Translated by DR. JOSEPH D. HEITER and DR. FRENCH K. HANSEL. Fifth edition; first English translation; two volumes. Pp. 701, 186 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $17.00.

IT is strange that this piece of work should have passed through four editions before being translated into English. The author, who was one of the pioneers in the field of sinus conditions, is the head of a Vienna clinic of world-wide reputation. Practically all English works on the subject have been greatly influenced by the observations of this clinic.

The present work of two volumes contains nothing new to the student of accessory sinus conditions, but covers the anatomy, pathology and surgery of these regions in detail. The anatomic studies which are so important to the rhinologist are especially good and are accompanied by an adequate number of illustrations. From the standpoint of pathology, the symptom complexes of the diseased

sinus conditions are well presented, as well as the gross morbid anatomy. The reports on microscopic studies of pathologic tissues are, however, rather meager, a feature which this work has in common with most other books on this subject. All the surgical procedures used today in the treatment of diseased sinuses are mentioned and their relative values stated. The large surgical experience of the author makes this portion of the book especially worth while. K. H.

A PRACTICE OF PHYSIOTHERAPY. By C. M. SAMPSON, M.D. Pp. 620; 146 illustrations. St. Louis: The C. V. Mosby Company, 1926. Price, $10.00.

THIS book is based on the author's previous work, *Physiotherapy Technic*, and is, like it, a very valuable contribution to the literature on physiotherapy. In addition to an excellent description of the physics and technic of the various applications, there is in this new volume much valuable information as to their use in a vast number of individual pathological conditions. The nature of the case and the aim of the treatment are constantly kept in mind. Description of apparatus and useful advice as to its proper care is also given.

The chapters on high frequency and actinotherapy are particularly well written, while altogether too small a space is devoted to those on massage and hydrotherapy to make them of much instructive value. J. N.

PRINCIPLES OF DIAGNOSIS AND TREATMENT IN HEART AFFECTIONS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D., Director of St. Andrews Institute for Clinical Research; Consulting Physician to the London Hospital, and JAMES ORR, M.B., CH.B., Physician to the St. Andrews Institute for Clinical Research. Third edition. New York: Oxford University Press, American Branch, 1926. Price, $3.50.

INTENDED originally as postgraduate lectures, the contents of this book were changed through war exigencies into a statement of recent advances in cardiology for the general practitioner. The author's increasing insistence on the proper study of function and his development of the clinical applications of the principle of the reflex arc receive sympathetic attention in Dr. Orr's revision. The four parts of the book (heart failure, disorders of mechanism, other heart affections and prognosis and treatment) summarize the teaching of the longer book, *Diseases of the Heart* (*vide* AM. J. MED. SCI., 1926, **171**, 593). E. K.

BOOKS RECEIVED.

Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1926. Pp. 330. Washington: Government Printing Office, 1926.

Report on Third International Congress of Military Medicine and Pharmacy, Paris, April 1925. By WILLIAM SEAMAN BAINBRIDGE, Commander Med. Corps, U.S.N.R.F. Pp. 111; 28 illustrations. Reprinted from the Military Surgeon, May to August, 1926.

Local Immunization. Specific Dressings. By A. BESREDKA. Translated by HARRY PLOTZ, M.D. Pp. 181. Baltimore: Williams & Wilkins Co.; 1926. Price, $3.50.

History Taking and Recording. By JAMES A. CORSCADEN, M.D. Pp. 78. New York: Paul B. Hoeber, Inc., 1926. Price, $1.50.

Diseases of Women. By HARRY STURGEON CROSSEN, M.D., F.A.C.S Sixth edition. Pp. 1105; 934 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $11.00.

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A Sound Economic Basis for Schools of Nursing. By MARY ADELAIDE NUTTING, R.N., M.A. Pp. 372. New York: G. P. Putnam's Sons, 1926. Price, $2.50.

A Statistical Survey of Three Thousand Autopsies. By WILLIAM OPHÜLS, M.D. Pp. 370. Stanford University, California: Stanford University Press, 1926.

Pneumoconiosis (Silicosis) A Roentgenological Study. By HENRY K. PANCOAST, M.D. and EUGENE P. PENDERGRASS, M.D. Pp. 186; 23 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $4.00.

On the Skull and Portraits of George Buchanan. By KARL PEARSON, F.R.S. Pp. 28; 11 illustrations. London: Oliver and Boyd, 1926. Price, Sixpence.

The Normal Child and How to Keep it Normal in Mind and Morals. By B. SACHS, M.D. Pp. 111. New York: Paul B. Hoeber, Inc., 1926. Price, $1.50.

Principles and Practice of Oral Surgery by Silverman. Pp. 326; 280 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $6.00.

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Ultra-Violet Rays in General Practice. By W. ANNANDALE TROUP, M.C., M.B., C.H.B. (ST. ANDREW'S). Pp. 59; 12 illustrations. London: H. K. Lewis & Co., 1926.

The Principles and Scope of Homœopathy. By JAMES W. WARD, M.D., F.A.C.S. Pp. 73. San Francisco: James W. Ward, M.D., University of California.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

An Experimental Study of the Synovial Fluid of Patients with Arthritis and Syphilis.—It is extremely difficult in the syphilitic to determine if an arthritis is the result of a syphilitic process or whether it is due to some other factor. CHESNEY, KEMP and BAETJER (*J. Clin. Invest.*, 1926, **3**, 131) undertook to ascertain if there were any characteristic changes of the joint fluid or any characteristic roentgenologic manifestations which would aid in the diagnosis of these lesions and, lastly, they endeavored to recover the specific organism, Spirochæta pallida, from the synovial fluid. They conclude that in its response to treatment the arthritis was syphilitic in origin in 5 cases. From the synovial fluid of 3 of these 5 patients strains of Spirochæta pallida which were virulent for rabbits were obtained by inoculation of animals of that species. In 4 of the 5 patients with syphilitic arthritis the fluid from the joint showed a relatively high percentage of lymphocytes and mononuclear cells combined. No significant roentgenologic changes were noted.

Angina Agranulocytotica.—ROCH and MOZER (*Presse méd.*, 1926, **74**, 1171) discuss the interesting condition which has recently been described by Schulz and about which but little has appeared in American literature. The condition of agranulocytotic angina most often occurs in women of middle age and is characterized by sudden onset, a grave infectious state, marked angina, frequently so severe as to be mistaken for diphtheria, and the all-important examination of blood which shows a considerable and marked diminution in the number of white blood cells, more especially of the granular, or polymorphonuclear cells. The lymphocytes and the monocytes in general are but little affected by this condition. The same statement applies to the red blood cells. The blood platelets also remain normal. In discussing the differential diagnosis the authors dismiss the possibility of mistaking the condition for almost any other condition associated with the same clinical syn-

drome by stating that septicemia, benzol poisoning, the leukemias and other similar conditions are not accompanied by such a pronounced fall in the white blood cells. Somewhat more difficult may be the diagnosis of arrested acute leukemia in the aleukemic phase and aplastic anemia. It is of interest to note the variety of changes in the blood pictures which occur with septic conditions of the mouth.

A Study of Sprue and Addisonian Anemia.—NEWHAM, MORRIS and MANSON-BAHR (*Lancet*, 1926, **211**, 269) present as a clinical study 90 cases of sprue which have been treated in the Hospital for Tropical Diseases, London, in the five-year period, beginning in 1920. The subject is presented from two points of view, from that of the clinician and that of the hematologist, and the subjective and objective symptoms of this condition are contrasted with those of pernicious anemia in the first part of the paper, while in the second portion the blood changes receive the same consideration. It is in the latter part of the paper that the newest material is presented. An extremely careful study of the blood in 12 cases of sprue is recorded, including hemoglobin estimations, count of the red cells and the white cells, estimation of the number of nucleated red cells, and the morphology of the erythrocytes. In addition to these usual studies, they have made Price-Jones curves of the red cells, studied the cholesterol content of the blood, studied the blood grouping in different cases and applied the van den Bergh reaction to the blood serum. The usual blood counts show that it is very hard indeed to make a differential diagnosis of these two conditions by the hematologist. A study of the red blood cell size and of the Price-Jones curves shows the close resemblance to those seen in pernicious anemia, with the exception that there is not such a marked variation in the size of the erythrocytes in the former as there is in the latter condition. The cholesterol content of the blood in both conditions shows that there is nothing to be gained from the viewpoint of differential diagnosis, as both of the two conditions show that there is a hypocholesterolemia. The anemia of sprue follows closely the behavior of pernicious anemia blood as applied to the van den Bergh reaction. The authors conclude that the two conditions are produced by two different and definitely opposite etiologic agents; that the anemia which accompanies the two diseases is almost identical but that the symptoms and physical signs vary considerably. They state dogmatically that the anemia does not indicate a similar or even allied etiology, despite the almost identical blood picture nor do they show by a statistical study that there is any very marked difference in the symptoms of the two conditions. The only definite evidence that they give that the two lesions are dissimilar is in the statement that of the 90 cases, all the patients had been in the tropics, although they add parenthetically that in 10 patients the disease had not developed until the return of the individual to Great Britain. In this country it is considered now that sprue is not essentially a disease of the tropics, but may occur in subtropical and temperate climates, so that their positive statement that all these cases occurred in the tropics and did not occur in England probably would have very much less weight in this country as proof of the duality of pernicious anemia and sprue than would be attached to such a statement in England.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Arthroplasty of the Hip.—BAER (*J. Bone and Joint Surg.*, 1926, **8**, 769) writes that arthroplasty for the production of motion in certain joints and under certain conditions has taken its place in surgery as a definite procedure. Arthroplasty for ankylosis of the jaw is an operative procedure as permanent and exact as is the operation of appendectomy. Next to the jaw, arthroplasty of the hip has made the greatest strides and is well on its way of taking its place as a recognized surgical procedure. The author feels that arthroplasty of the hip for gonorrheal arthritis is not only a proper procedure, but it almost assures the patient of good motion in the hip. He would not hesitate to recommend such procedure to any patient applying for relief. The results of arthroplasty in traumatic ankylosis of the hip are very gratifying. Prognosis in septic infection of the hip should be far more guarded. It is difficult to tell what changes have been made in the human body by the previous continuous suppuration. Here one is dealing with latent fire. In tuberculous arthritis caution should be the motto. Opinion is generally against an arthroplasty. In some adults, apparently cured, but with exacerbation of fluid in the joint and its consequent disability, good results may be obtained. In arthritis deformans the procedure should not be used.

Giant-cell Tumor of Bone.—GOFORTH (*Arch. Surg.*, 1926, **13**, 846) says that the known behavior of the giant-cell tumor warrants its being classified as a true neoplasm. The giant-cell tumors constitute a series. Those at the lower end of the scale possess relatively adult fibrous stromas and are essentially benign. Recurrences are more aggressive or virulent than the primary growth both clinically and microscopically. They are potentially malignant and may as a result of repeated or improper treatment undergo malignant transformation and metastasize. The giant cells or osteoclasts that are characteristically present function as bone absorbers and are of osteoblastic origin. They are not reliable indexes of the neoplasm's relative malignancy. The stroma is of fibroblastic origin, and its behavior governs the course of the giant-cell tumor. Through microscopic study of its cellularity, cell type and cell activity offers a fairly reliable criterion of the innocence or relative malignancy of the growth. History, thorough clinical and Roentgen ray study, and a rigid follow-up, are all necessary in establishing the final correct diagnosis and the true nature and behavior of the giant-cell tumor.

The Mortality Rate in Appendicitis—Is it on the Increase?—MARSH (*Boston Med. and Surg. J.*, 1926, **195**, 1059) states that reference to the leading surgical clinics in this country reveals the fact that the mortality of major operative conditions is decreasing, while in the hands of the average surgeon the mortality, with the exception of pelvic conditions, shows a decided increase. However, the evidence of increased mortality rate as given out by the Bureau of Vital Statistics may be misleading and an apparent increase may be explained in other ways. Statistics from some of the hospitals of New England rather indicate that in that part of the country the rate is decreasing. It is from the advanced case that the mortality comes. There may be a surgical accident in any case or postoperative adhesions may cause mechanical ileus. There is the occasional wrong diagnosis and the frequently delayed diagnosis. Indifference to or ignorance of the significance of abdominal pain on the part of the patient, causing delay, is the greatest factor in raising the rate. To a less degree the procrastination of the doctor enters into it, and even less than either is the skill of the operator.

Bursitis of the Plantar Surface of the Foot.—HERTZLER (*Am. J. Surg.*, 1926, **1**, 117) claims that the association of gonorrhea with exostoses and painful affection of the feet has not been proven. The association of pain in the feet with stretching of ligaments rests on the assumption of sensitiveness of ligaments. This conclusion was arrived at by a process of exclusion and is contrary to the facts. Certain painful affections of the feet occur in regions where bursæ are known to exist. The clinical manifestations are similar to those of bursal inflammations in other parts of the body. Obliteration of these bursæ by operation cures the patient. Operations based on other hypotheses (that is, exostosis) do not cure the patient unless the bursæ are inadvertently obliterated.

Diffuse Gastric Polyposis.—BRUNN and PEARL (*Surg., Gynec. and Obst.*, 1926, **43**, 599) say that diffuse gastric polyposis is seemingly a rare disease, since the authors have only been able to collect 84 cases from the literature. They do not feel, however, that these figures represent the true incidence of the disease. The condition may be either congenital in origin or arise from an inflammatory basis. It is of interest that these tumors have been reproduced experimentally. The symptoms and physical signs are not characteristic. Achylia is the most significant finding. Combined with fresh blood and abundant mucus it should suggest the diagnosis. Malignant degeneration occurred in 12 per cent of the 84 cases collected. The treatment should be surgical. It is of interest that in our own and in the collected series no case of pernicious anemia has developed in spite of continued achlorhydria. In the authors' series 1 case lasted twenty-five years.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK.

Treatment of Postencephalitic Parkinsonianism of Nicotin.—MOLL (*Brit. Med. J.*, 1926, 1, 1079) reports 13 cases of postencephalitic Parkinsonian disease in which he used hypodermic injections of the pure alkaloid of nicotin to counteract the increased muscle tone and consequent apparent stiffness of joints. It was thought that, since the sialorrhea, rise in pulse rate and retraction of eyelids were signs of increased sympathetic stimulation, possibly the muscle tonicity was at least in part due to this same cause. McAlpine has described degenerative changes in the substantia nigra in the midbrain and in the anterior part of the globus pallidus of the lenticular nucleus. These lesions were thought to possibly interfere with the normal prespinal reflex arc and thus result in an increased plastic tone of the muscles. Nicotin paralyzes the the preganglionic sympathetic cells, and thus might block the sympathetic prespinal arc. The treatment was initiated with doses of $\frac{1}{80}$ gr., three times a day. This was usually followed by a fall in pulse rate, then a rise with a return to normal in seven to ten minutes. The blood pressure also showed a gradual rise with a return to normal in about the same time. Other phenomena observed were flushing of the face, profuse sweating, tremors, thirst, nausea, vomiting and tachypnea. In 2 cases a fit with tonic spasm and loss of sphincter control followed by vomiting was noted. This initial dosage was kept up for a few days, until no untoward symptoms occurred, then it was gradually increased to $\frac{1}{10}$ or $\frac{1}{5}$ gr., three times a day, and continued for two to three weeks or until signs of intolerance appeared. Nine of the 13 cases were helped by this treatment, stating that "their joints felt looser." Of the other 4, 1 was a true Parkinsonian and was not helped and the other 3 seemed to derive no benefit at all. The action was only temporary, after six months time all the patients being just as badly off as before. The author concludes that nicotin is of temporary aid due to paralyzing the prespinal reflex arc subserving plastic tone and that the injections should be repeated every two to three months. The other symptoms, such as sialorrhea and tremors, were influenced in no way at all.

The Treatment of Intestinal Hemorrhage.—Also in *Monde médical* (October 1, 1926) there is an abstract of an article by TURPIN from *Progrès médical* on the treatment of intestinal hemorrhage: (1) In slight hemorrhage, rest, champagne and iced milk; subcutaneous injection of the posterior lobe of hypophysis or of 1 cc. of the following solution: Ergot, 2 gm.; glycerin and water, each 5 gm.; every half hour a teaspoonful of the following: Calcium chlorid, 4 gm.; syrup of opium, 30 gm.; water, 120 gm. (2) In severe hemorrhage, absolute

rest flat in bed; ice to the abdomen; nothing by mouth; subcutaneous abdominal injection of 500 cc. of artificial serum; every half hour a teaspoonful of the mixture mentioned above and two or three injections of posterior lobe of hypophysis in twenty-four hours. (3) In very severe hemorrhage with collapse and loss of consciousness, intravenous injection of 1 gm. of adrenalin, $\frac{1}{1000}$, in 300 gm. of water and 2 gm. of sodium chlorid. In cases where adrenalin is contraindicated he recommends the intravenous injection of 500 cc. of isotonic glucose associated with the subcutaneous injection of chloralhydrate of emetin. Also slow lavage with warm water containing 4 gm. of calcium chlorid, and again posterior lobe of hypophysis intravenously. In hemorrhages due to an alteration of the blood he uses subcutaneous whole blood, horse serum or transfusion.

The Intravenous Use of Hexamethyl Amine in Typhoid Fever.—In *Monde médical* (October 1, 1926) there is an abstract of an article by CHALIER and GRANDMAISON, published in *Progrès médical*, dealing with the intravenous use of hexamethyl amine (urotropin) in typhoid fever. These writers state that if the drug is injected just prior to or during the stage of bacteremia its bactericidal effect will tend to lessen the possibility of growth or organisms in the blood stream and their consequent spread to the various organs. As the urotropin is excreted in the bile and in the urine its use tends to reduce the complications of cholangitis and posttyphoid cholelithiasis and to lessen the number of urinary typhoid carriers. They have not seen a nephritis develop from its use, and think that albuminuria is no contraindication. In those cases where it has been used early in the disease the complication of intestinal hemorrhage seems to have been reduced.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

The Effect of Various Supplementary Lunches on the Plasma Carbon Dioxid Capacity of Children.—MORGAN and HATFIELD (*Am. J. Dis. Child.*, 1926, **32**, 655) made carbon dioxid capacity studies on 12 children upon whom they made other studies of nutrition. Five of these children were from 5 to 17 per cent underweight, according to the Baldwin and Wood Standard, 1 was 33 per cent overweight and 6 were practically normal in weight. The 6 normal children showed alkaline reserve figures of 42 to 65 per cent or cubic centimeters of carbon dioxid per 100 cc. of plasma. Four of the 5 underweight children showed corresponding values of 38 to 51. One child who was given figs as a supplementary lunch gained more than three times the expected

amount in weight, and showed an increase of 5.5 per cent in carbon dioxid combining power of plasma after a period of forty-three days. Five children who were given oranges as a supplementary lunch, and upon whom two or three alkaline reserve determinations were made at twenty-eight to fifty-day intervals showed increase in carbon dioxid combining power of plasma of 1.7 to 11.19 per cent. Those subjects who failed to make the expected gain in weight during these periods also showed the lowest gains in alkaline reserve. Two out of 3 children who were changed from oranges to milk after a twenty-eight day interval showed a decrease in alkaline reserve of plasma of from 3 to 7.78 per cent. The third child showed an increase of 1.37 per cent after a forty-three day interval on milk. Whether the alkaline reserve values observed were indicative of a cumulative relatively steady rate of change or were variable random figures modifiable within a few hours by a change in diet is a question which can be definitely answered only by day to day observations on a number of subjects.

Breast Feeding Problems.—Moore and Dennis (*J. Am. Med. Assn.*, 1926, **87**, 1970) emphasize that to overcome the mental hazards of motherhood regarding breast feeding physicians must stress the fact that every mother who can care for her baby can nurse it. They also point out that daily health routine of the lactating mother needs more careful study and regulation by the physician. The amino acid and vitamin B content of the diet are very important. During this period a milk diet is very inadequate. Abnormal constitutional conditions, including contagious diseases in the mother may necessitate artificial feeding for a time, but the glands should be kept active by manual expression, so that the breast feeding may be restored at the earliest possible moment. Open tuberculosis in the minds of the authors is the only absolute indication for weaning. Premature weaning is at present too frequently the result of remediable conditions in the mammary glands. Breasts and nipples deserve a complete examination, including inspection, palpation and milk expression. Nipple muscle hypertrophy and hypertonicity are curable. Aseptic care of the nipples together with the use of nipple aërators prevents infections, fissures and mastitis. Aërators evaginate everted nipples and permit the necessary open air treatment. The cancer fear, as an excuse for avoiding nursing or manual expression is refuted by experience and by statistics. Manual expression is the best means of improving an insufficient maternal supply.

The Effects of Diet on Rickets.—Greenebaum, Selkirk, Otis and Mitchell (*J. Am. Med. Assn.*, 1926, **87**, 1973) report a study of the effects of actively regulating diets of pregnant women on the development of rickets in their offspring. These observations were made on 25 women who had previously had rachitic children, and the period of observation covered both winter and summer seasons. One mother whose infant did not develop rickets was 1 of 2 in whose diet throughout the last months of pregnancy there were approximated the standard sought. In the infant of this other mother rickets was not found until after the eighth month. The average daily caloric intake of the mothers whose infants developed moderate and marked rickets were as a group lower than in the group whose infants developed mild rickets. In the

entire series, regardless of the degree of rickets, the mineral intake of the mothers was approximately the same. In those cases in whom blood examinations were made the inorganic phosphorus content of the blood obtained in the antepartum period was uniformly normal, while the inorganic phosphorus content of the babies' blood was below normal, The calcium content of both mothers' and babies' blood was normal. A low calcium content of the breast milk was often found, and this possibly was the result of the inadequate diets of the mothers during the lactation period, since practically all of them returned during that time to the previous habits of eating, consuming a diet in which milk, especially, was lacking. The inorganic phosphorus of the breast milk was uniformly normal. The season of the year in which the babies was born apparently had no influence on the degree of rickets, although an absolute conclusion cannot be reached on account of the small number of cases in the series. Five of the babies found by Roentgen ray to have rickets had no clinical evidence of the disease. Two babies whose Roentgen ray studies were negative for rickets were considered to have rickets clinically. The incidence of rickets in this group of 22 babies to whom cod liver oil was not given was as follows: By the eighth month 16 showed rickets on clinical examination, or 73 per cent, and 19 showed rickets by Roentgen ray examination, or 87 per cent. As the result of this study, the authors feel that if the diet of the mother during the last three months of pregnancy can be made approximately correct in caloric and mineral intake, while it will not prevent rickets, it will have a controlling influence in the development of the disease in the child.

Scarlet Fever.—Platou and Collins (*Arch. Pediat.*, 1926, **43**, 707) report that small doses of 3000 skin test doses of scarlet fever toxin detoxified with sodium ricinoleate did not protect 8 nurses who were exposed to the disease from three to seven weeks after receiving the injection. Among individuals that are kept Dick negative by inoculation or reinoculation with the same preparation in larger doses there were no cases of scarlet fever in spite of intimate exposure. Increasingly large initial doses of toxin may prevent the necessity of reinoculation in order to preserve immunity. The administration of a total of 9000 skin test units of Larson's detoxified preparation rendered a large percentage of children Dick negative for a period of a year. The commercial preparations of scarlet fever antitoxin used in a comparative study of 190 cases were apparently specific. Acceleration in clinical improvement as gauged by temperature, rash and symptoms was quite definite in 100 cases receiving the antitoxin. This was especially true in those to whom antitoxin was administered early. Better results might have been obtained if larger initial doses of antitoxin graded in units according to the blanching power per cubic centimeter could have been given. When given early the serum has a beneficial effect on the toxemia and seems also to reduce the number of complications, although no effect on septic processes was noticeable. The small prophylactic doses given to 5 cases in this group did not prevent later infection with scarlet fever. In one-fourth of the cases serum sickness was an annoying factor and in 11 cases it was extremely discomforting to the patient, especially in those who had been sensitized previously to horse serum through diphtheria immunization.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

CLEVELAND J. WHITE, M.D.,

ASSOCIATE IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF BUFFALO, BUFFALO, N. Y.

On the Urticarial Reaction and its Physiologic Meaning.—This is essentially a summary of the joint work of GRANT (*Brit. J. Dermatol. and Syph.*, 1926, **38**, 425) with Sir Thomas Lewis on a recent interpretation of the physiologic meaning of the urticarial reaction. There is a type discrepancy between the dilution of histamin mentioned in Grant's article and the dilutions used by Sir Thomas Lewis in other reports, the former speaking of 1 in 30,000 and the latter of 1 in 3000. Lewis and the author believe that the urticarial reaction is a type of defense mechanism on the part of the skin which is uniform for every form of trauma, including mechanical injuries, such as stroke, prick and scratch; burning heat; cold and freezing; galvanic currents; ultraviolet light; chemical substances, including hydrochloric, lactic and formic acids, morphin, atropin, cantharidin and many other substances; antigens in subjects susceptible to the protein concerned. This urticarial reaction takes place upon the liberation of a theoretical histamin like substance in the "traumatized" skin. They base this belief upon the essentially identical character of the reactions produced by the stroke and by the pricking of histamin in a dilution of 1 to 3000 into the skin. In both cases a red line or red spot appears in about twenty seconds, which is best seen when the veins are slightly congested. In persons who exhibit a dermographism a wheal appears along the stroke, and around the pin prick in the case of the histamin. If the venous pressure in the arm be raised sufficiently to close the arterial circulation no wheal appears, although the red spots develop, indicating that the latter is a vasoparetic phenomenon. The flush is arterial in origin and is controlled by the nervous system through a local nervous reflex, which persists even when the nerves to the skin are freshly divided, although it disappears when the cutaneous nerves have degenerated (not dependent on a spinal reflex arc). The wheal develops as a consequence of increased permeability of the vessel walls, as shown by Ebbecke, who found that trypan red injected into the circulation would not pass through the vessel walls unless an injury had taken place. The authors believe the increased permeability to be independent of the nervous system, because it will appear on anesthetized skin. The reactions of the histamin and the stroke wheal to changes in venous pressure, heat and cold are practically identical.

The third argument advanced by the authors for the identity of the histamin and other types of wheal formation is the establishment of *refractoriness*. If the appearance of the wheal is prevented by arresting the circulation for fifteen minutes or more no subsequent wheal formation can be obtained, even though more histamin be introduced into the previously pricked area. The failure of the wheal to appear and the failure of response to further stimulation, constituting refractoriness, occurs in all the forms of wheal excitation mentioned above. The authors believe that factitial urticaria is due to an exaggerated susceptibility of the cells of the skin, which respond to mechanical injury by release of a diffusible substance. The work of Hare and Lewis and a number of his coworkers is cited in support of these statements. This group of observations is of particular interest because it again brings into the field of causation of cutaneous inflammatory reactions the histamin hypothesis proposed by HARRIS in 1916 (*Arch. Dermatol. and Syph.*, 1921 **3**, 579). This author proposed on theoretical grounds that histamin acting as the antagonist of adrenalin was capable of explaining the clinical picture of eczema, including the vascular phenomenon and the itching inseparable from that condition. Thus far, of course, the influence of histamin is largely a matter of inference, inasmuch as no such substance has been identified in any of the local lesions involved. Its formation in other parts of the body, however, and its possible absorption into the blood may provide a basis for further investigation and verification of this significant hypothesis.

OBSTETRICS

UNDER THE CHARGE OF

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA,

AND

CLIFFORD B. LULL, M.D.,

CLINICAL ASSISTANT IN THE OBSTETRICAL DEPARTMENT, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Retrodisplacement of the Uterus during Pregnancy and the Puerperium.—DANFORTH and GALLOWAY (*J. Am. Med. Assn.*, 1926, **87**, 826) set forth the findings of a large number of cases during pregnancy and following labor. About 20 per cent were found to have retrodisplacements, and the authors consider that retrodisplacement as a pathologic entity has been overemphasized. They believe far too many operations are performed for the correction of the displaced uterus. In certain cases of sterility they believe displacement the causative factor. The operative treatment is not discussed. The

routine examination in the early months of pregnancy makes known the fact of the position and the movability of the uterus. If retrodisplaced, it is left in this position, subsequent examinations determining whether it has risen out of the pelvis or whether it has been prevented in so doing by incarceration below the promontory. Manual replacement is ordinarily undertaken. The Schultz method is used if the manual reposition fails and a pessary is put in place suitable to hold the uterus in position until the growth of the uterus is assured; so that it cannot again become retrodisplaced into its old position. The displacement of the uterus provides an intelligent observation, being carried out during pregnancy. A large proportion of the retrodisplaced uteri correct themselves spontaneously. The large majority can be manually replaced without anesthetic and held in position by mechanical measures. About 14 per cent of the retrodisplacements of uterus during pregnancy become retrodisplaced in the puerperium.

Etiology and Diagnosis of Intrauterine Fetal Death.—Browne and Kincaid (*J. Am. Med. Assn.*, 1926, **87**, 847) report on experimental work on a case and brings out a probable cause of intrauterine fetal death during pregnancy. Those cases which have formerly been classified as idiopathic can, in all probability when fetal syphilis, fetal anomalies, toxemias of pregnancy and acute maternal infections are ruled out, be laid to direct infections of the fetus itself. The case reports and case experimental studies are given in detail. The article suggests that in a clinically healthy mother a fetus may apparently succumb in *utero* to a hematogenous streptococcal infection.

Trial Labor in the Treatment of 477 Cases of Contracted Pelvis.—Bailey (*Am. J. Obst. and Gynec.*, 1926, **12**, 550) deals with a large number of cases covering a period of four years and conducted under one plan of treatment. It covers the mortality of Cesarean section in a number of states of the mothers and infants following a careful canvass and the results of a questionnaire in the trial labor; all pelves with the true conjugate below 7 cm. are called absolutely contracted, and should be delivered by elective section. All other patients of this series with relatively contracted pelves, with the exception of those who were previously Cesareanized were given trial labor. The trial labor consisted in allowing the patients to have twelve hours of strong pains without rectal or vaginal examination. If at the end of this time the head was floating, a low section was performed; if the head was in the pelvis the patient was delivered by permitting the labor to continue and using forceps. The article classifies the pelvic contractions of the pelvis into minor and major, according to the diameter of the true conjugate. The funnel pelvis and irregular contractions are also tabulated. As an end result the author sets forth the maternal death rate as 0.42 per cent and an infant death rate of 4.19 per cent. The author clearly shows in the series of cases that trial labor in relatively contracted pelves reduces the incidence of operation and results in a minimum mortality for mother and child, provided that when a Cesarean section is necessary the low operation be performed.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Cancer of the Cervix.—In his survey at the University of California Hospital during the past ten years, LYNCH (*Surg. Clin. North America*, 1926, **6**, 333) has treated nearly 400 pelvic cancers, and he has a fairly good follow up review on which to base his opinion of the results. His experience has demonstrated to him that the ordinary panhysterectomy with the removal of the adnexa is useless from the standpoint of cure, because the growth is insidious and has usually extended beyond the confines of the uterus when operation is attempted. The ordinary hysterectomy cannot be radical except in the rarest of cases, since the ureters so closely parallel the sides of the upper cervix, where the lymphatic circulation is most abundant. He has never seen a cure of squamous cell epithelioma of the cervix where the diagnosis was apparent to the naked eye. The few cures that he has seen from ordinary hysterectomy were limited to cases in which the disease was microscopic in character and presented no definite lesion to the eye. While he believes, like most other surgeons at the present time, that radium offers the best prospect of relief in most cases of cervical cancer, nevertheless in the early cases he still feels that the extended operation is the method of choice. He has done 49 radical operations, with a mortality of 8 per cent, this series including cases which were primarily operable and those which were inoperable when first seen but which were treated and made operable by radium. Of the 16 primary operable cases which have survived five years, there are 8, or 50 per cent, which apparently are cures. At the present time, therefore, he is of the opinion that all the truly operable cases that are good risks should be operated upon after preliminary radiation, while all the other cases should be treated by radium alone. In support of the radical operation, he states that those who survive the operation are far more likely to escape a cancer death than those treated by radium, while those who die from the operation are saved from the more hideous cancer death. He warns again attempting to operate upon any of the cases in the so-called borderline group.

Treatment of Sterility by Roentgen Ray Therapy.—In a recent contribution to the subject of sterility, to which subject he has previously contributed such important work, RUBIN (*Am. J. Obst. and Gynec.*, 1926, **12**, 76) discusses his experience with the use of Roentgen ray therapy in the treatment of that type of sterility which is associated

with habitual amenorrhea. This therapy is based on the supposition that the Roentgen ray exercises an irritating effect upon unfunctioning ovaries when applied in small dosage, although it has also been considered that the irradiation causes a regressive change in a persisting corpus luteum which has been the factor in prolonging the amenorrhea. In a rather large experience Rubin has found that habitual amenorrhea is associated with sterility in about 5 per cent of cases. Pregnancy takes place in about 5.5 per cent of the untreated cases. In 9 out of 12 cases treated with mild doses of Roentgen ray pregnancy resulted (that is, 75 per cent of the treated cases). Only 1 of these patients aborted. The rest carried to full term and gave birth to normal children. Roentgen ray irradiation of the ovaries resulted in restoration of the menses in 11 out of 12 cases of amennorrhea. Rontgen ray irradiation of the hypophysis area and the thyroid appears to have an adjuvant value. Two of the pregnant cases and 2 of the nonpregnant cases received hypophyseal irradiation. One of the pregnant cases also received thyroid irradiation. Peruterine tubal insufflation and endocrine therapy are additional aids to the therapeutic action of the Roentgen rays in cases of amenorrhea associated with sterility. As the ovaries were found to be definitely enlarged before treatment in 8 of the 9 successful cases treated with Roentgen rays, careful examination with regard to this point may prove of aid in selecting the cases or amenorrhea associated with sterility suitable for ovarian stimulation. When no ovarian enlargement is found irradiation to the hypophyseal area or the thyroid, etc., may be more advisable, and should certainly precede irradiation of the ovaries.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,
HEAD OF THE SCHOOL OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Arterial Pressure in the Eye.—DUKE-ELDER (*J. Physiol.*, 1926, **62**, 1) constructed an apparatus to measure directly by means of a manometer the pressure within the central artery of the retina and its branches. Five experiments on cats gave an average systolic pressure of 88.5 mm. of mercury; diastolic, 64 mm. of mercury. Mean pressure interpreted as $\frac{S+D}{2}$ = 76 mm. of mercury in the ophthalmic artery. The intraocular tension was 24 mm. of mercury. Taking the point of maximal pulsation as a diastolic and that of the cessation of pulsation as the systolic pressure, the result of a series of six experiments by an oscillatory method gave for the systolic pressure within the posterior ciliary arteries 115 mm. of mercury; diastolic, 78.5 mm. of mercury; $\frac{S+D}{2}$ = 97− mm. of mercury. Intraocular tension was 25 mm. of

mercury. The carotid pressure was 106 mm. of mercury. He assumes that in the ciliary body the arterial mean pressure is about 75 mm. of mercury, that the venous pressure is about 25 mm. of mercury, while the intraocular pressure is about 24 mm. There is thus a fall in the vascular system of about 50 mm. of mercury. In man he assumes that the pressure gradient from the arteries to veins is more than 50 mm. of mercury. When it is remembered that the intraocular pressure is 20 to 25 mm. of mercury it would seem that the arterial and venous pressures in the eye bear a relation to the chamber pressure similar to that which the vascular pressures do to the tissue pressure throughout the body generally. The tissue lymph contains about one-half the quantity of colloids that are found in the blood, while the aqueous is practically protein free. Consequently, if the fluids of the eye can be formed without the intervention of a "secretory" mechanism the capillary pressure in the eye must exceed the intraocular pressure by more than the difference that obtains generally between capillary and tissue pressure. In round figures, a difference of 30 mm. of mercury must exist in the eye instead of 15 mm. elsewhere. There is every indication that this may be so. In the first place, the ciliary arteries seem to be anatomically peculiar in that they break up almost at once into a rich network of capillaries which appear to be capable of rising to a considerable height. Again, the veins are physiologically constricted at their exits from the eye, and the whole system is confined under a considerable tension within a feebly distensible case, the sclerotic, which will make the vessels approximate in their behavior to a system of rigid tubes. These considerations will all tend to throw the site of the fall of pressure further toward the veins and make it probable that the pressure in the arterial capillaries rises at least 30 mm. of mercury higher than in the chamber of the eye, that is, to a total of about 50 to 55 mm. of mercury. The vascular pressures, therefore, although by themselves they prove nothing, make it possible that the aqueous humor is formed purely by a process of dialyzation.

Blastomycosis of the Cornea with a Review of Reported Cases of Blastomycosis of the Eye.—McKee (*Int. Clin.*, 1926, **3**, 50) was consulted by a man, aged forty-three years, because of involvement of the eyes in a blastomycotic infection of the face and neck which had been present for three years. While shaving he cut a small pimple on his left cheek. Within a week he noticed a small raised area about the size of a pin. This spread slowly at first, then quickly, involved the left lower eyelid, then went across the nose to the right lids, under the ear and under the chin. The right lids were completely involved in irregular papilla-like elevations from which pus oozed upon slight pressure. The lids on the left side were practically gone. Besides a large leukoma there was found on the cornea of the left eye an ulcerative process. Smears from the conjunctiva were negative, but those from the cornea showed typical blastomycosis. The corneal ulcer healed very quickly with ordinary measures. General condition improved promptly under the administration of potassium iodid.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

The Pathology of Deaf Mutism.—"In the first decade of our century, when this research became known, it was supposed that certain alterations were characteristic of deaf mutism, just because similar changes were found in the labyrinth of congenitally deaf animals, for example, the Japanese dancing mice, albino cats and dogs, etc. Later on, however, it was shown that analogous abnormalities may exist also in cases of simple deafness. This may exist also in cases of simple deafness. Furthermore, similar anomalies were described in experimental labyrinth pathology and to this discovery we owe much insight into the pathogenesis of inner-ear diseases. It may be added that in isolated cases histologic research did not result in finding any local changes. It is supposed, therefore, that there must exist anomalies of the central connections and the brain. The pathology of deaf mutism for this reason does not represent something that is entirely confined to the labyrinth of the deaf mute. In the same way the conception of deaf mutism, though accepted generally as a clinical term, scientifically is not correct because, according to Bezold's hearing tests, in fact only a small number of so-called deaf mutes are totally deaf; the latter belong mostly to the acquired forms of deafness." Limiting himself solely to deaf mutism and its local manifestations in the ear, NAGER (*Laryngoscope*, 1926, **36**, 313) emphasizes the importance of the central lesions and their histologic changes. In acquired deaf mutism the results are, as a rule, those of inflammatory processes in the labyrinth, whether meningitic, tympanic or hematogenic in origin. Deaf mutism caused by meningitis has been known longest and best. In such cases a new formation of bone and connective tissue of varying degrees up to complete obliteration of the labyrinth cavities occurs. If the cochlear duct is preserved it will show important changes, such as collapse, dilatation or adhesions. Corti's organ is missing, as are the cells of the stria vascularis. The membrana tectoria is often enclosed in an epithelial capsule. The spiral ganglion and nerve fibers are absent. In lymphatic labyrinthitis very extensive destruction or complete obliteration of the labyrinth is found, not infrequently coupled with cholesteotoma. The pathology of congenital deaf mutism is much more many-sided. In the endemic congenital type one deals with one of the symptoms of endemicretinic degeneration, where there is a marked hyperostosis of the promontory, with a narrowing of the window inches and adhesions of the deformed stapes. In the cochlea a small hyalin body embedded between the organ of Corti and the membrana tectoria is found. In sporadic deaf mutism the changes are exclusively in the labyrinth, usually bilateral. They

have been regarded as malformations, ranging from the rare absence, through the slighter change in the neuroepithelium of the scala media, to the sacculocochlear degenerations, which comprise 70 per cent of sporadic congenital deaf mutes with remnants of hearing and include most of the constitutional hereditary form. Here, again, different grades of development are observed—those with defective central axis and those with large dilations of the saccus endolymphaticus. Besides these forms very marked malformations of the cochlea may exist, as the presence of only 1.5 coils instead of the normal 2.5 coils. It is very interesting to observe that tuning-fork examination revealed defects even in the inferior tone limit in cases in which the upper cochlear coils were absent. In a considerable number of these cases the bony labyrinths showed distinct spots of otosclerosis.

The Early Signs of Cancer of the Esophagus.—According to GUISEZ (*Presse méd.*, 1926, **34**, 964), dysphagia of solid food is an early and characteristic sign of esophageal cancer. On the other hand, fluids and soft food may be swallowed with ease, in contradistinction to the discomfort encountered when similar substances are ingested in spasm of the gullet. When the carcinoma occurs in the upper portion of the esophagus, a symmetrical white or black coating at the base of the tongue, lateral to the median raphé, is the rule. While blood-streaked sputum suggests an esophageal neoplasam, a single attack of hematemesis is often seen in esophagospasm. The diagnosis can be clarified by esophagoscopy and biopsy. The author states that radium is of value in the treatment of esophageal malignancy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Imbibition of Dyes by the Aortic Wall.—Intravenous injections of colloid solutions of trypan blue and carmin, as well as lipoids, have been shown to form deposits on the aortic wall by several workers. OKUNEFF (*Virchow's Arch. f. path. Anat.*, 1926, **259**, 685) thought he would be able to arrive at conclusions regarding the origin of arteriosclerotic changes by injecting 1 per cent solutions of trypan blue by various routes into different types of animals. He gave these injections subcutaneously, intraperitoneally, intravenously, into the stomach and into an intestinal loop, and also varied the length of time that the

animals were exposed to the dye. It was found that the flecking of the aortic wall and its localization occurred in rats, mice and rabbits, but was not so characteristically similar to the conditions found in the human as was that in cats and dogs. The areas of imbibition were found to give support to Virchow's view, that the stagnation of the blood plasma determines the site, namely, at the branchings of the innominate and subclavian arteries, at the ductus arteriosus, at the coronary sinuses, in the region of the semilunar valves and along the descending aorta at the orifices of the intercostals. The subcutaneous and intraperitoneal routes gave staining in two to three hours and gave a maximum response with the dye in contrast to the slow and poor-staining produced by the enteral injections. The intima showed the greatest amount of dye, but penetration into the elastic layer was also noted. The flecking found by using dyes was analogous to that found in cases of arteriosclerosis and also to localization of lipoids in children, as well as to the results after experimental injection of lipoids. The origin of the pathologic changes in the aorta seems to be from the chronic absorption of fat mixtures in the intestines, which are transported to the aorta through the blood stream. The sites of deposition are doubtless decided by mechanical factors as well as to the localization of the lymph circulation, that is, there is a heaping of the lipoids at the points of greatest diffusion of plasma from the bloodvessel into the lymph stream.

Hemochromatosis and Chronic Poisoning with Copper.—MALLORY (*Arch. Int. Med.*, 1926, **37**, 336) has been making a study of cirrhosis of the liver, and in analyzing the cases occurring in the Boston City Hospital he finds they can be divided into five groups: Infective, biliary and syphilitic, toxic, alcoholic and the pigment cirrhosis. The latter has occupied his attention recently, inasmuch as experimental work with rabbits and monkeys has confirmed his opinion that chronic copper poisoning is the true etiology of hemochromatosis and bronzed diabetes. The same type of lesion was found in the animals as in the autopsy material. Furthermore, a study of the clinical side of the cases showed that nearly two-thirds of the group were exposed over long periods to copper either through alcohol made in copper worm stills or through their occupations. A considerable number of the group were shown to be exposed, through canned fruits or other foods and drinks. It would seem that evidence is steadily accumulating in favor of the view that chronic copper poisoning causes the symptom complex known as hemochromatosis, pigment cirrhosis or bronzed diabetes.

Primary Carcinoma of the Liver.—It would appear from the recent work of COUNSELLER and MCINDOE (*Arch. Int. Med.*, 1926, **37**, 363) that primary carcinoma of the liver only occurs in about 0.08 per cent of all autopsies. They report 5 cases and find that 4 of these 5 appeared to rise from the liver cell itself while the other appeared to have arisen from the cells lining the finer bile canaliculi. Males predominated. The usual clinical diagnosis was cirrhosis of the liver, and it has now been shown that very rarely is primary carcinoma of the liver not preceded by cirrhosis, which probably forms one of the predisposing factors to the malignancy. The gross appearance of these two types

of liver carcinomata varies, being massive, nodular and diffuse. No apparent relation exists between the gross and microscopic pictures, though the massive form is usually derived from the liver cells. Metastases occur in both types, but are usually intrahepatic, that is, into the portal and hepatic veins. It would appear that the origin of these growths is unicentric, as no transitional forms were found. All the cases were associated with cirrhosis of the portal type. Probably 3 to 4 per cent of such cases of cirrhosis result in carcinomata.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Further Studies on a Diplococcus from Measles; Prevention of Measles by Immune Goat Serum.—TUNNICLIFF and HOYNE (*J. Inf. Dis.*, 1926, **38**, 48) state that the serum of a goat convalescing from a resection produced by the inoculation of green-producing measles diplococci protected rabbits against a subsequent injection of infective material from measles. The rabbits injected with normal goat serum and those untreated showed some or all of the characteristics of measles in rabbits—a rise of temperature, Koplik spots and an eruption. Convalescent goat serum protected human beings against measles as effectively as convalescent human measles serum when injected on the first and second days after exposure to measles. By intracutaneous tests in normal rabbits the serum of goats injected with diplococci from measles, as well as convalescent human measles serum, were shown to neutralize the action of killed measles diplococci, while serum of normal goats had no such effect. The serum of one immune goat was found toxic to nearly all persons injected with it, but after eight months preservation it appears to have lost its toxic effect. While these experiments do not furnish conclusive evidence of the protective value of immune goat serum, they warrant further investigation.

Some Nutrition Experiments with Brewers' Yeast.—SMITH and HENDRICK (*Pub. Health Repts.*, 1926, **41**, 201) present the following conclusions, after giving details of the experiments leading to these conclusions: Dried brewers' yeast contains some factor essential in nutrition other than vitamin B. This factor withstands autoclaving

at 15 pounds' pressure for six hours. It is not in the heat and acid coagulable yeast protein. It is capable of adequately supplementing a ration in which the oat kernel is the sole source of protein and vitamin B. Evidence is advanced to show that a synthetic ration with casein as the sole source of protein must be supplemented with this unrecognized factor present in yeast, besides vitamin B, in order to make it adequate. When properly supplemented, oat protein appears to be just as satisfactory in the nutrition of the rat as is casein protein.

Four Cases of Tularemia (Three Fatal) with Conjunctivitis.—FREESE, LAKE and FRANCIS (*Pub. Health Repts.*, 1926, **41**, 369) report an outbreak of tularemia due to the eating of undercooked rabbit by a family living in southwestern Virginia. The fatality rate was extraordinarily high—3 of the 4 cases dying. The onset was sudden, with fever, headache, vomiting, chills and in 1 case convulsions. Soon the temperature rose to 103° to 104° F., and there developed conjunctivitis, with swelling in the region of the parotid, bilateral in all but 1 case; later cervical and axillary glands became swollen and the picture was one of extreme febrile intoxication. A culture of the causative organism was secured from nasal swabbings after passage through a guinea pig, and the blood serum from the case which recovered gave agglutination with Bacterium tularense. The 3 fatal cases had been buried before the nature of the disease was suspected. An experiment on a rabbit dead of tularemia showed that in spite of apparently satisfactory cooking the infection might remain in the deeper parts.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 20, 1926

The Selective Absorption of Normal Goat Serum.—J. D. ARONSON (from the Laboratory of the Henry Phipps Institute of the University of Pennsylvania). Fresh normal goat serum produces necrosis when injected into the dermis or into the subcutaneous tissue of normal guinea pigs. When injected directly into the general circulation or into the peritoneal cavity death results. Furthermore, the addition of fresh normal goat serum to washed guinea pig cells hemolyzes these cells. It seemed likely that these differences in the results obtained from injecting the serum into different parts might depend upon the fixation of the serum by the different tissues. Experiments were undertaken to determine whether there existed a selective absorption by the different tissues for the hemolysin, necrotizing substance and toxic substance of normal goat serum.

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The organs of normal guinea pigs were ground in a mortar with salt

solution, filtered through gauze and washed. To varying amounts of the washed tissue cells 2 cc. of fresh unheated goat serum were added, and the mixture of cells and serum shaken for two hours at 37° C. After centrifugalizing, the supernatant serum was collected and tested for its hemolytic action on guinea pig cells and for its necrotizing and toxic action on guinea pigs.

It was found that while the adrenal, heart, voluntary muscle and spleen did not absorb the hemolytic or necrotizing substance, the liver, kidney, skin, testes and erythrocyte stroma absorbed the hemolysin and necrotizing substance. The brain and lungs showed some absorption of the hemolysin and absorbed completely the necrotizing substance. The toxic substance was absorbed by suspensions of kidney, liver and testes, but not by the spleen.

When suspension of the different guinea pig tissues were heated at 70° C. or higher for thirty minutes, or were heated at 100° C. for ten minutes, their ability to absorb the goat serum hemolysin and necrotizing substance was decreased or destroyed completely.

It was found that erythrocytes of rats and mice were relatively resistant to the hemolytic action of normal goat serum, and that these animals were insusceptible to the necrotizing and toxic action of normal goat serum. Suspensions of the spleen, brain, liver, kidneys and testes of rats prepared in the same manner as those from guinea pigs were unable to absorb the hemolysin present in normal goat serum.

The fixation of the hemolysin to the kidney or liver cells is a firm one, and the hemolysin could not be dissociated from the cell by extracting with salt solution, distilled water, 0.1 per cent sodium carbonate or by freezing and thawing.

Studies of Gastric Acidity in Infants.—J. STOKES, JR., and J. TATUM (from the Department of Pediatrics of the Medical School of the University of Pennsylvania). The present studies of gastric acidity followed a comparison of the electrometric and colorimetric methods for determination of the pH of gastric contents (*J. Biol. Chem.*, 1926, **69**, 75) and studies of the alteration in pH of the gastric contents after passage of the stomach tube in subjects with gastrostomies (*Am. J. Dis. Child.*, 1926, **32**, 667). The object of the present studies was to examine by the electrometric method the pH of gastric contents obtained with as little gagging or contamination with saliva and mucus as was possible. Attempts to make normal infants regurgitate their meals with slight stimulation of the gagging reflex were usually unsuccessful. Certain specimens of gastric contents were obtained readily by gagging, but the great majority were obtained by passage of a catheter through the nose, assisted by pressure on the abdomen, the entire process consuming a relatively short period. By this method, in which the quantity of gastric contents compared favorably with the amounts obtained by other methods, it was felt that the alkaline diluents, which usually contaminate the gastric contents obtained by the ordinary use of stomach tube with the suction of a syringe, were practically eliminated, and that more accurate values for the pH of the gastric contents were found.

The pH of the gastric contents of newborn infants before the administration of milk or water averaged 1.6, the lowest value found being pH 1.026.

In normal infants under ten days of age the average pH of the gastric contents obtained one to one and a half hours after breast feedings was 2.9. This figure would have been low, except for 3 or 4 subjects whose gastric contents showed consistently a pH of about 5.0.

In normal infants of ten days to six months of age the average pH of gastric contents obtained in this way was 3.9.

An infant suffering from lobar pneumonia was found to be an interesting subject for study, since the slightest stimulation of his gagging reflex would evacuate apparently his entire gastric contents. His gastric contents were examined from the second day of his illness to the sixth day of his convalescence. Increased acidity of the gastric contents followed definite lowering of the temperature early in the disease, and the crisis of the pneumonia was followed by an elevation of the acidity which persisted. The cause or causes for such changes are not known.

The Absorption of Fat Through the Skin of the Newborn Rat.—W. H. F. Addison and D. A. Fraser (from the Department of Anatomy, University of Pennsylvania). The clinical use of ointments and salves dates from ancient times, but the study of how fat is absorbed is a recent one and is still incomplete. According to current conceptions, when a fatty substance is rubbed on the skin it is partly pressed into the hair follicles and sweat glands, and absorption takes place chiefly through the epithelium of the sebaceous glands and of the ducts of the sweat glands. In order to study histologically the absorption of fat through skin, newborn rats were used. In these there are no sweat glands, the hairs have not yet appeared and the hair follicles are in an early stage of development. In the epidermis there are already differentiated three strata—corneum, granulosum and germinativum. In the stratum corneum is a variable number of layers of swollen empty cells, as in the fetal skin. In the granulosum are three or four rows of cells, with numerous keratohyalin granules at the poles of the horizontally directed nuclei. The stratum germinativum is also three or four rows in thickness, and forms a uniform zone, except where it is continued inward as the developing epithelial hair follicles. The underlying connective tissue is highly cellular and contains many vessels.

When lanolin is applied to the skin of newborn rats it passes through the cells of the epidermis into the tissues of the corium. At the end of a half hour it can be demonstrated histologically by fat stains in all these tissues and apparently in the superficial bloodvessels. In order to see whether the fat within the blood was possibly due to the animal having suckled, the blood of animals to be experimented upon was first examined by the darkfield microscope. In animals which had suckled there were numerous chylomicrons in Brownian motion within the plasma, but in animals which had not suckled no chylomicrons were seen.

Our observations show that in the skin of newborn rats there is direct absorption of fat through the surface epithelium into the deeper tissue. In accordance with current theories of the nature of plasma, membranes

and protoplasm, it is indicated that the fat probably passes in by spreading along the lipoid protein interfaces of the protoplasm of the cells.

Afferent Nerve Impulses from Muscular Receptors.—G. P. McCouch, A. Forbes and H. L. Rice (from the Laboratories of Physiology of the Medical School of the University of Pennsylvania and of Harvard University). Afferent nerve impulses from muscular receptors were recorded from the peripheral portion of the cut peroneal nerve of the cat by Forbes, Campbell and Williams (*Am. J. Physiol.*, 1924, **69**, 283). The stimulus employed was the contraction of the tibialis anticus muscle in response to a single break shock to the nerve. Three oscillations (designated *b*, *c* and *d*), due to groups of proprioceptive impulses, followed the stimulating action current.

The object of the present work was the correlation of these groups of proprioceptive impulses with changes in the muscle. Records were made under both isometric and isotonic conditions. Action currents from nerve, tension upon the tendon and movement of the foot were synchronously recorded upon the same film. The time relations and a comparison of the amounts of tension, of movement and of action currents developed under various degrees of limitation of movement indicate that the *b* wave is associated with initial rise of tension; the *c* wave is associated with movement; the *d* wave is associated with the rise of tension occurring at the terminal slowing of movement, when the momentum of the descending foot puts the flexor tendons upon a stretch.

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